STUDIES ON THE REACTIONS OF C-HETERO BOND FORMATION

A Thesis Submitted to the University of North Bengal
For the award of
Doctor of Philosophy (Ph.D)
in
Chemistry

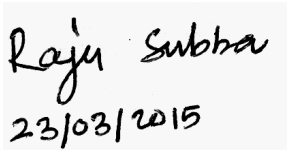
By
Raju Subba (M.Sc)

Research Guide
Dr. Pranab Ghosh (Associate Professor)
Department of Chemistry
University of North Bengal
(2015)

Dedicated to my parents....!!

DECLARATION

I declare that the thesis entitled "STUDIES ON THE REACTIONS OF C-HETERO BOND FORMATION" has been prepared by me under the guidance of Dr. Pranab Ghosh, Associate Professor, Department of Chemistry, University of North Bengal, Darjeeling-734013. No part of this thesis has formed the basis for the award of any degree or fellowship previously.



Raju Subba
Department of Chemistry
University of North Bengal
Darjeeling – 734 013
India

Date: 23.03.2015

UNIVERSITY OF NORTH BENGAL

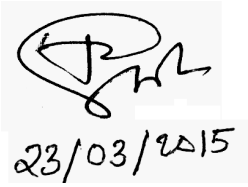
Dr. P. Ghosh
Associate Professor
DEPARTMENT OF CHEMISTRY
University of North Bengal
Darjeeling – 734 013, India.

Ph: +91 3532776 381 (off)
+91 9474441468 (M)
Fax: +91 353 2699 001
Email: pizy12@yahoo.com

Date: 23.03.2015

CERTIFICATE

This is to certify that Mr. Raju Subba has prepared the thesis entitled "**STUDIES ON THE REACTIONS OF C-HETERO BOND FORMATION**" for the award of Ph.D degree of the **University of North Bengal,** under my guidance. He has carried out the research work at the Department of Chemistry, University of North Bengal, Darjeeling, West Bengal-734013.



Dr. Pranab Ghosh (Research Supervisor)
Associate Professor
Department of Chemistry
University of North Bengal
Darjeeling-734013
India

Date: 23.03.2015

Acknowledgement

This thesis is a compilation of my research work carried out under the supervision of Dr. Pranab Ghosh, Associate Professor, Department of Chemistry, University of North Bengal during the period of 2009 to 2015. It comprises the studies on the reactions of C-hetero bond formation.

The successful completion of my research work is credited to the guidance of my esteemed supervisor Dr. Pranab Ghosh, Associate Professor, Department of Chemistry, University of North Bengal, without whose help and support I would have never finished my research work successfully and would remain as a dream. I offer my heartfelt gratitude for his valuable suggestions and for his support. Therefore I consider it as a great honour to work with Dr. Pranab Ghosh.

This thesis is a culmination of all the courses and experiments that I pursued during the tenure of my five years research work at the Department of Chemistry, University of North Bengal (NBU). I would therefore like to thank all the faculty members of the Department of Chemistry, University of North Bengal who have greatly supported me during my research work. I would like to extend my sincere thanks to all the non-teaching staff of the Department of Chemistry, University of North Bengal, for helping me in all possible ways.

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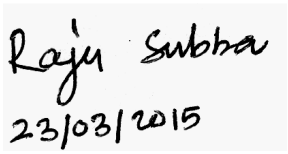
In addition, a sincere thanks to all my friends, sisters and brothers of North Bengal University, for always being there for me and helping me in all possible ways.



Raju Subba
Department of Chemistry
University of North Bengal
Darjeeling-734013
West Bengal

Abstract

Chapter I: General introduction of carbon-heteroatom bonds

The backbone of many organic compounds is composed of C–C bonds, but the function of these molecules is often derived from the presence of heteroatoms, such as nitrogen, oxygen and sulphur, which are held in these molecules by C–heteroatom bonds. Although, C-heteroatom bond forming reactions is thermodynamically much more favourable than C-C cross coupling reactions, C-heteroatom bond formation has occupied unique site in organic chemistry. For example, most of the pharmaceuticals often contain C–N bonds and almost all natural products contain C–O bonds. Heterocyclic compounds in which C–N, C–O or C–S bonds are present in the ring structure are found in all applications of chemistry. Extensive work has been done on exploring the importance of C-hetero bond towards the biological, synthesis and designing new class of drugs and material properties associated with these classes of compounds. The huge importance and broad scope of carbon-hetero bond create a keenness to author to carry out the methodological work for carbon-heteroatom bond forming reactions.

Chapter-II: Selective epoxidation of steroidal skeleton by *m*-chloroperbenzoic acid (*m*CPBA)

Section –A: Chapter II (section-A) deals with methodical literature review on epoxide, its synthesis and *m*CPBA. Epoxide is considered as useful intermediate for the synthesis of wide range of compounds with biological interest. Epoxidation of olefins can be carried out with various catalytic systems. *m*CPBA is well known reagent for the epoxidation and rearrangement of various types of natural and synthetic substances. The detail literature survey reveals that there is still a requirement of easy, green and new protocols for the epoxidations.

Section – B: Chapter II (section-B) deals with the selective epoxidation of 16-dehydropregnenolone acetate (16-DPA) by m-chloroperbenzoic acid (*m*CPBA). The epoxidation of 16-DPA by *m*CPBA on activated silica at room temperature furnished only 5, 6-monoepoxy derivative but the same reaction in $CHCl_3$ under reflux condition offered 5, 6-16, 17-diepoxy derivative. The reaction on activated silica was extended to β-sitosterol, β-sitosterol acetate and β-sitosterol benzoate and found good result.

Chapter-III: Solid phase synthesis of oxime derivatives

Section –A: Chapter III (section-A) deals with methodical literature review on oxime, synthesis and its applications. Oximes are considered as a versatile organic intermediate for the synthesis of wide range of organic compounds. Classically, oximes were prepared by refluxing an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride and pyridine. The multiple drawbacks of classical method gave birth to the development of modern method for their preparation. The modern methods comprise the synthesis of oximes from diverse functional groups under varied reaction conditions. The need of new methodologies was come up due to various draw-backs of existing methodologies.

Section –B: Chapter III (section-B) deals with the selective oximation of carbonyl compounds by hydroxylamine hydrochloride on silica under solvent free conditions. The 1, 2 aromatic dicarbonyl compounds furnished exclusively monoxime at room temperature and dioxime at elevated temperature. The aromatic aldehydes, alicyclic carbonyl also offered excellent yield. The aromatic ketones furnished no yield at room temperature but offered excellent results at elevated temperature. No selectivity was found in alicyclic 1, 2 and 1, 3 dicarbonyl compounds.

Chapter-IV: $FeCl_3$ mediated one-pot transformation of aldehydes into nitriles

Section –A: Chapter IV (section-A) deals with methodical literature review on nitriles, synthesis and its applications. Nitriles are considered as important intermediate for the functional group transformation and heterocyclic synthesis. During the last decades, use of various catalytic systems has been established for the oxidative transformation of nitrile from various functional groups. The demand and need of new protocols were come up owing to various draw-backs of existing methodologies.

Section- B: Chapter IV (section-B) deals with the ferric chloride mediated one-pot transformation of aromatic aldehydes into nitriles. The reaction were carried out by adding aldehyde (1 mmol) and hydroxylamine hydrochloride (1.2 mmol) to a solution containing anhydrous ferric chloride (0.5 mmol) in 5 ml dry DMF. The excellent yields of desired products were obtained under reflux condition. All aromatic aldehydes furnished good to excellent yield except the aldehyde having electron withdrawing group which furnished comparatively lower yield.

Chapter-V: $MgCl_2.6H_2O$ catalyzed synthesis of 2-substituted benzimidazoles

Section –A: Chapter V (section-A) deals with methodical literature review on benzimidazoles, synthesis and its applications. Benzimidazole is an important substructure found in many pharmaceuticals. Numerous methodological works has been done to prevail over the draw-backs of classical methods. The comprehensive literature review reveals that there is still a need of straight forward method for the synthesis of benzimidazoles.

Section –B: Chapter V (section-B) deals with $MgCl_2.6H_2O$ catalyzed synthesis of 2-aryl or heteroaryl substituted benzimidazole derivatives from 1, 2-phenylenediamine and aryl or heteroaryl aldehydes. The reaction mixture was stirred on magnetic stirrer at 60 ^oC for appropriate time to furnish desired products. The aliphatic aldehydes do not provide any product. The poor reactivity of aliphatic aldehydes might be because of possible enolization of carbonyl.

Chapter-VI: Synthesis of substituted imidazoles on titanium incorporated silica solid support

Section –A: Chapter VI (section-A) deals with methodical literature review on imidazole, synthesis and its applications. Imidazole is regarded as important substructure found in many bioactive compounds. In view of the diverse applications associated with these derivatives, the development of more convenient synthetic protocol is highly encouraging. The detail literature review reveals that numerous protocols has been developed under varied catalytic system but there is still a paucity of green and cost efficient protocol for the synthesis of imidazole derivatives.

Section –B: Chapter VI (section-B) deals with the synthesis of tri- and tetra-substituted imidazole on titanium incorporated silica solid support under solvent free conditions. The synthesis were carried out by mixing titanium incorporated silica intimately with benzil/benzoin, aromatic or hetero-aromatic aldehydes and ammonium acetate under solvent free conditions. The desired products were obtained at 90 ^oC. The solid support was recycled and used up-to five consecutive reaction runs. The detail quantification of titanium on silica by electron diffraction X-ray spectroscopy before and after recycling suggested that no significant loss of titanium from silica. The solid support was found equally applicable for the synthesis of tetrasubstituted imidazoles.

Preface

The multiple purpose, broad scope and high significance of C-heteroatom bond create a keenness to author to carry out the methodological based work on C-heteroatom bond forming reaction. C-heteroatom bond has occupied distinctive position in organic chemistry as far as its medicinal value and material properties concern. Most of the pharmaceuticals often contain C–N bonds and almost all natural products contain C–O bonds. Heterocyclic compounds in which C–N, C–O or C–S bonds are present in the ring structure are found in all applications of chemistry. Extensive research has been done on exploring the importance of C-hetero bond in the area of biological chemistry by designing new class of drugs and material properties associated with these classes of compounds.

The area of C-heteroatom bond forming reactions has experience an enormous application due to their wide range of application in designing the compound with chemical or biological interest. Numerous works have been done and substantial amount of new methodologies have been developed for their synthesis. Most of the reported methodological works are not straight-forward, easy or environmentally benign. The development of new methodologies is still going on to reach the mild and green approach for the sustainable development. As there are numerous varieties of compounds having carbon-heteroatom, the methodological based works on some of them are covered in this thesis. This thesis covered the synthesis of epoxy-derivatives of few steroids by *m*CPBA on silica or $CHCl_3$, selective synthesis of mono and dioximes on silica, $FeCl_3$ mediated organo nitrile synthesis, $MgCl_2.6H_2O$ catalyzed synthesis of 2-substituted benzimidazoles and synthesis of substituted imidazole on titanium-silica solid support. The unique structural or biological features of these selected carbon-heteroatom compounds prompted author to carry out the present methodological work.

The major aim of this thesis is to offer new literature on methodological work on carbon-heteroatom bond forming reaction. The new methodologies described in this thesis are mild, cost-effective, environment friendly which definitely meet the present demand under the aspect of green and sustainable development.

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Appendix A

List of Published/Accepted/Communicated research papers

1. Studies on the reaction of 16-dehydropregnenolone acetate (16-DPA) With *m*-chloroperbenzoic acid

   Pranab Ghosh[*] and Raju Subba. *Journal of the Indian Chemical Society*. 89, **2012**, 1733-1735.
2. Green and highly selective protocol for the synthesis of oximes

   Pranab Ghosh* and Raju Subba. *Journal of the Indian Chemical Society*. 90, **2013**, 529-532.
3. Reductive Coupling of Benzaldehyde Mediated by Camphor

   Alok Majumdar, R. Subba, P. Ghosh, and A. K. Nanda.* *Journal of Chemical and Pharmaceutical Research*. **2012**, 4(4):2261-2262.
4. $FeCl_3$ mediated one-pot route to nitriles

   Pranab Ghosh[*] and Raju Subba. *Tetrahedron Letters*. **2013**, 54, 4885–4887.
5. $MgCl_2.6H_2O$ catalyzed highly efficient synthesis of 2-substituted-1H-benzimidazoles

   Pranab Ghosh[*] and Raju Subba. *Communicated to Tetrahedron Letters*. [Ms. Ref. No.: TETL-D-14-02836]
6. Titanium incorporated silica: a new recyclable solid support for efficient synthesis of substituted imidazoles.

   Pranab Ghosh[a*] Raju Subba[a], Abiral Tamang[b], Bittu Saha[a] and Gyan Chandra Pariyar.[a] *Communicated to RSC Advance*. [Ms. Ref. No.: RA-COM-03-2015-003761]

Appendix B

List of research papers presented in preceding seminars

1. Green and highly selective protocol for the synthesis of oximes

   Raju Subba and Pranab Ghosh.* National Seminar on Frontiers in Chemistry 2011 and Celebration of the International Year of Chemistry 2011. (March 14-16, 2011), Department of Chemistry, University of North Bengal, Darjeeling. (Oral presentation).

2. $MgCl_2.6H_2O$ – As an Efficient Alternative Catalyst for the Synthesis of 2-Substituted Benzimidazoles

   Raju Subba and Pranab Ghosh.* UGC Sponsored National Seminar on Frontier of Chemistry. (November 15-16, 2011), Department of Chemistry, Gour Mahavidyalaya, Malda. (Oral presentation).

3. $FeCl_3$-Silica: A highly efficient, solvent free and reusable heterogeneous system for the facile synthesis of pyrazine

   Raju Subba, Amitava Mandal and Pranab Ghosh.* 13^{th} CRSI National Symposium in Chemistry. (February 4-6, 2011), National Institute of Science Education and Research (NISER) and KIIT University, Bhubaneswar. (Poster presentation).

4. Cost effective catalyst free synthesis of 2, 4, 5-trisubstituted- 1H- imidazoles

   Raju Subba and Pranab Ghosh.* Chemical Research Society of India Eastern Zonal Meeting 2011 and Celebration of the International Year of Chemistry 2011. (July 22-24, 2011), Department of Chemistry, University of North Bengal, Darjeeling. (Poster presentation).

Appendix C

Abbreviations

$FeCl_3$	Ferric chloride	TS-l	Titanium silicalite
$CHCl_3$	Chloroform	WO_3	Tungsten trioxide
HCl	Hydrochloric acid	Al_2O_3	Aluminium oxide
$ZnCl_2$	Zinc Choride	CH_3CN	Acetonitrile
DMF	N,N-Dimethylformamide	Bi_2O_3	Bismuth(III) oxide
$(NH4)_2S$	Ammonium sulfide	Na_2SO_4	Sodium sulphate
DMSO	Dimethyl sulfoxide	KBr	Potassium bromide
$AgNO_3$	Silver nitrate	$Cu_2(OTf)_2$	Copper I triflate
PTFE	Polytetrafluoroethylene	KCN	Potassium cyanide
H_2SO_4	Sulfuric acid	CuCN	Cuprous cyanide
OIPh	Iodosylbenzene	$NaHCO_3$	Sodium bicarbonate
TAPC	Triphosphazene	KOH	Potassium hydroxide
NBS	N-bromosuccinimide	TMS	Tetramethyl silane
$NaBH_4$	Sodium borohydride	I_2	Iodine
MeOH	Methanol	DCE	Dichloroethane
MoO_3	Molybdenum oxide	Me_3SiN_3	Trimethyl silyl azide
$NiCl_2$	Nickel chloride	H_2O_2	Hydrogen peroxide
NaN_3	Sodium azide	THF	Tetrahydrofuran
$FeCl_2$	Ferrous chloride	PIDA	Phenyliodine diacetate
KI	Potassium iodide	$CuSO_4.5H_2O$	Copper suphate hydrate
$[Os(N)O_3]^-$	Nitridoosmate	$Fe(ClO_4)_3$	Iron III perchlorate
BuONO	tert-Butyl nitrite	$Fe(OTf)_3$	Iron III triflate
Ti	Titanium	NH_4OAc	Ammonium acetate
PEG	Polyethylene glycol	SPB	Sodium perborate
CAN	Ceric ammonium nitrate	ABM	Animal Bone Meal
$SnCl_2$	Stannous chloride	PPA	Polyphosphoric
$Yb(OTf)_3$	Ytterbium III triflate	PbO_2	Lead IV oxide
CuI	Cuprous iodide	CuBr	Cuprous bromide
MnO_2	Manganese oxide	Cu_2O	Cuprous oxide
$NaHSO_3$	Sodium bisulfite	$In(OTf)_3$	Indium III triflate

$Na_2S_2O_5$	Sodium metabisulfite	$Sc(OTf)_3$	Scandium III triflate
$KHSO_4$	Potassium bisulfate	$Cu(OTf)_2$	Copper II triflate
$ZrCl_4$	Zirconium IV chloride	CuO	Cupric oxide
$Sm(OTf)_3$	Samarium III triflate	H_2O	Water
PBI	Polybenzimidazole	$HClO_4$–SiO_2	Perchloric acid-silica
$BF_3.SiO_2$	Boron trifluoride-silica	Fe_3O_4	Iron oxide
TFA	Trifluoroacetic acid	$TiCl_4$	Titanium tetrachloride
$TiCl_3$	Titanium trichloride	$Cu(NO_3)_2$	Cupric nitrate
mL	Milliliters	^oC	Degree celsius
Temp	Temperature	h	Hour
Min	Minutes	Mp	Melting point
ppm	Parts per million	mmol	Millimole

16-DPA	16-dehydropregnenolone acetate
$MgCl_2.6H_2O$	Magnesium chloride hexahydrate
*m*CPBA	Metachloroperbenzoic acid
DDQ	2, 3-Dichloro-5, 6-dicyano-1, 4-benzoquinone
TCT	2, 4, 6-trichloro-1,3,5-triazine
$NH_2OH.HCl$	Hydroxylamine hydrochloride
nBu_4NI	Tetra-n-butylammonium iodide
DBU	1, 8-Diazabicyclo[5.4.0]undec-7-ene
PCBS	poly(N, N′-dichloro-N-ethylbenzene-1, 3-disulfonamide
TCBDA	N, N, N′, N′-tetrachlorobenzene-1, 3-disulfonamide
$Fe(BF_4)_2.6H_2O$	Iron (II) tetrafluoroborate hexahydrate
TBAF	Tetrabutylammonium fluoride
$FeSO_4.7H_2O$	Ferrous sulfate heptahydrate
TBAB	Tetrabutylammonium bromide
$Fe(NO_3)_3.9H_2O$	Iron III nitrate nonahydrate
$(NH_4)_2Fe(SO_4)_2.6H_2O$	Ferrous ammonium sulfate hexahydrate
$NH_4Fe(SO_4)_2.12H_2O$	Ammonium ferric sulfate dodecahydrate
TBHP	tert- Butyl hydroperoxide
DBSA	dodecylbenzenesulfonic acid

TEMPO	2, 2, 6, 6-Tetramethylpiperidine 1-oxyl
DMEDA	N, N-Dimethylethylenediamine
$PhI(OAc)_2$	(Diacetoxyiodo) benzene
p-TSA	Para-toluenesulfonic acid
$K_5CoW_{12}O_{40}\cdot 3H_2O$	potassium dodecatugstocobaltate trihydrate
$[(CH_2)_4SO_3HMIM]$	3-Methyl-1-(4-sulfonicacid)butylimidazoliumhydrogen
$[HSO_4]$	sulphate
DABCO	1, 4-Diazabicyclo[2.2.2]octane
SEM	Scanning electron microscope
TLC	Thin layer chromatography
FT IR	Fourier transform infrared spectroscopy
NMR	Nuclear magnetic resonance
EDX	Energy-dispersive X-ray spectroscopy

CHAPTER-I

General introduction

CHAPTER-I

General Introduction

I.1. A brief introduction of C-hetero bond

The backbone of many organic compounds is composed of C–C bonds, but the function of these molecules is often derived from the presence of heteroatoms, such as nitrogen, oxygen and sulphur, which are held in these molecules by C–heteroatom bonds. Although, C-heteroatom bond forming reactions is thermodynamically much more favourable than C-C cross coupling reactions, C-heteroatom bond formation has occupied unique site in organic chemistry. For example, most of the pharmaceuticals often contain C–N bonds and almost all natural products contain C–O bonds.

Heterocyclic compounds in which C–N, C–O or C–S bonds are present in the ring structure are found in all applications of chemistry. Inspite of these, C-heteroatoms containing compounds has ability to stabilize the metals ions through ligation or complexation in both biological and non-biological system, for example, magnesium and iron in chlorophyll and haemoglobin are stabilized by nitrogen ligands. There are various organic compounds having carbon-hetero bond which shows important catalytic activities for the various organic transformations. The well known organocatalyt composed of carbon-heteroatom bonds are crown-ethers, quaternary ammonium salt (eg.tert-butyl ammonium bromide) called phase transfer catalyst which promotes the complicated organic transformation in a easier way by stabilizing the metal ions through ligation.

I.2. Objectives and scope of the thesis

The area of C-heteroatom bond forming reactions has experience an enormous application due to their wide range of application in designing the compound with chemical or biological interest. Numerous works have been done and substantial amount of methodologies have been developed for their synthesis. Most of the reported methodological works are not straight-forward, easy or environmentally benign. The development of new methodologies is still going on to reach the mild and green approach for the sustainable development. As there are numerous varieties of compound having carbon-heteroatom, the methodological based work on some of them is

embodied in this thesis. The thesis covered the synthesis of epoxy-derivatives of few steroids by *m*CPBA on silica or $CHCl_3$, selective synthesis of mono and dioximes on silica, $FeCl_3$ mediated organo nitrile synthesis, $MgCl_2.6H_2O$ catalyzed synthesis of 2-substituted benzimidazoles and synthesis of highly substituted imidazole on titanium-silica solid support. The unique structural or biological features of these selected carbon-heteroatom compounds prompted author to carry out the present methodological work.

The major aim of this thesis is to provide new methodological work for the synthesis these useful compounds by carbon-hetero bond forming reaction. The new methodologies described in this thesis are mild, cost-effective, environment friendly which definitely meet the present demand under the aspect of green and sustainable development.

I.3. Brief review of the compounds described in this thesis

I.3.1. Biological profile of compounds having carbon-hetero bond

Carbon-heteroatom functionality is an important structural feature in most of the biologically active compounds. For example, 5, 5'-substituted indirubin-3'-oxime derivatives (**1**,**2**) found potent cyclin-dependent kinase inhibitors with anticancer activity.[1] Vildagliptin (**3**) is amino-nitrile containing antidiabetic drug in which the nitrile bearing carbon is not fully substituted, letrozole (**4**) is the aromatase inhibitor for the treatment of breast cancer (**fig. I.1**).[2]

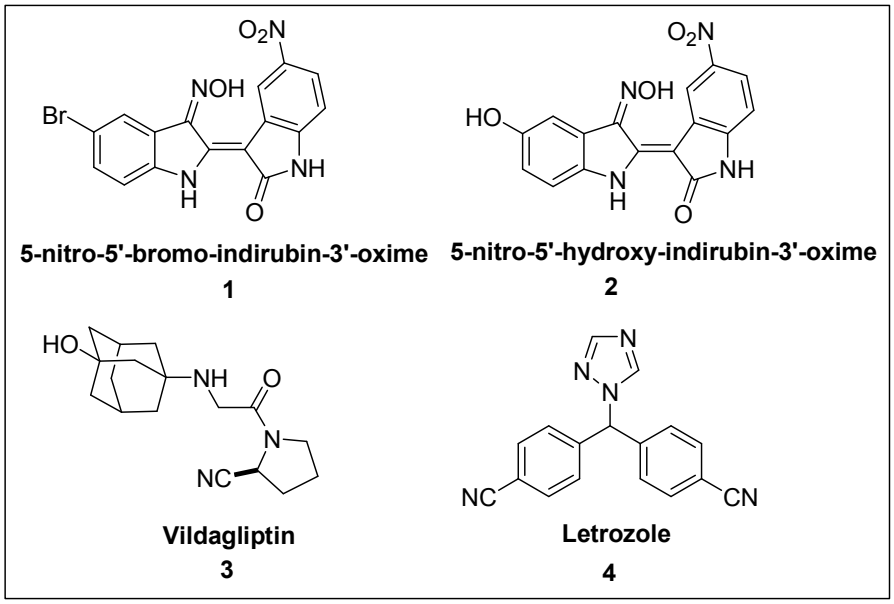


Fig.I.1. Biologically potent drugs having carbon-heteroatom bonds

Carbon-nitrogen bond containing heterocycle has also remarkable medicinal value with respect to their inhibitory activity and their favourable selectivity ratio. Extensive biochemical and pharmacological studies have confirmed that these classes of moiety are effective against various strains of microorganisms. One of the carbon-nitrogen containing heterocycle called benzimidazole and its derivatives are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin-B_{12}. This ring system is present in numerous bioactive compounds having antiprotozoal,[3] antihelmintics,[4] anti-HIV,[5] anticonvulsant,[6] antiinflammatory,[7] antihepatic,[8] and antineoplastic,[9] antiulcer,[10] activities. Many of these derivatives are widely used for the treatment of parasitic diseases. One of the first drugs representing these compounds, now widely used in helminthology, was mebendazole (**fig. I.2.)**

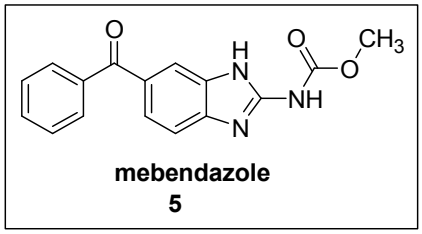


Fig.I.2. Mebendazole

At present, more than twenty of these derivatives are used as antihelminth preparations in the world veterinary and medical practice, including flubendazole (**6**), oxfendazole (**7**)**,** fenbendazole (**8**), trifenagrel (**9**) (**fig.I.3.**). Another heterocycle containing carbon-nitrogen bond is imidazole which is strongly associated with many important biologically active molecules. The most important is the amino acid histidine which has an imidazole side chain. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of haemoglobin. The suitable substitutions of these derivatives are valuable in treatment of many systemic fungal infections. Imidazoles belong to the class of azole antifungals or treatment for the parasitic deceases.

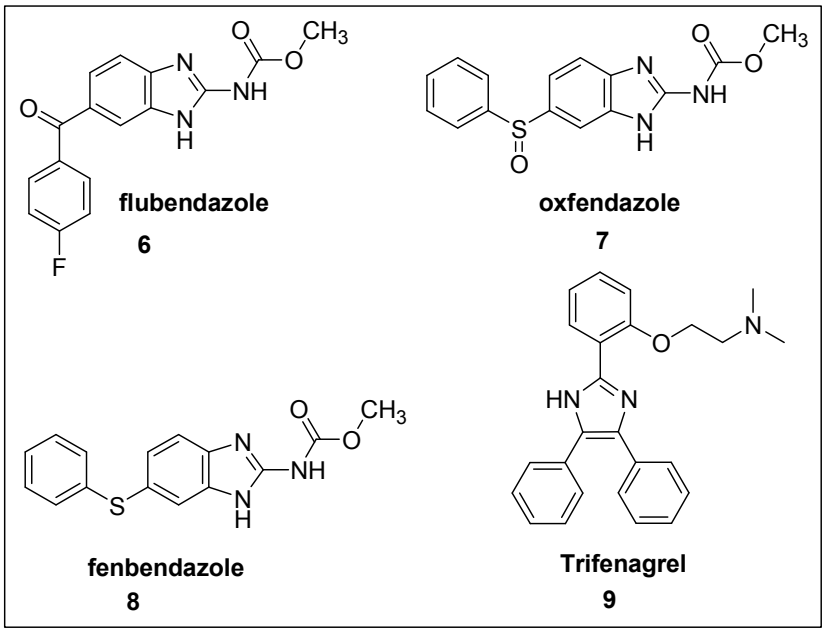


Fig.I.3. Examples of benzimidazole and imidazole drugs

I.4. Application of carbon-hetero bond containing intermediate in organic synthesis

I.4.1. Application of epoxide in organic transformations

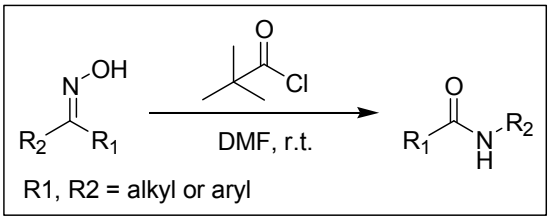
Epoxides are considered as versatile intermediates in organic synthesis, which are susceptible to nucleophilic attack to form the substituted hydroxyl products.[11] Ring

opening of epoxides with nucleophilic reagents is an useful tool for the preparation of several 1, 2-disubstituted

products.[12] Literature review revealed that substantial amount of organic transformation have been carried out with epoxides for the preparation of wide range of organic compounds.[13-17]

I.4.2. Application of oximes in organic transformations

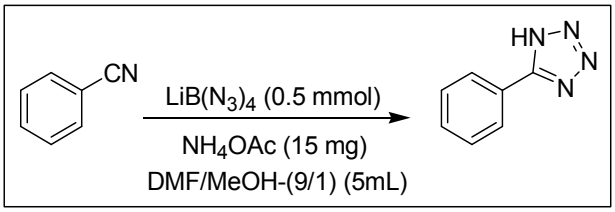
Oximes are used extensively for the protection of carbonyl function. This compounds not only represents the series of derivatives of carbonyl compounds but also used as useful intermediate for the important organic synthesis and functional group transformations. Particularly, the manufacture of cyclohexanone oxime represents a key step in the sequence of the nylon 6 production. Inspite of having a huge industrial and medicinal uses, the other important and interesting application of oximes is functional group transformations and synthesis of nitrogen containing heterocycles such as Beckmann rearrangement for the synthesis of amide from ketoxime. Recently reported advance methodologies for the preparation of amide from ketoximes includes, cyanuric chloride catalyzed Beckmann rearrangement of ketoximes into amides under mild condition with HCl and $ZnCl_2$ as effective cocatalyst,[18] perfluoroalkylsulfonyl fluoride-mediated abnormal Beckmann rearrangement for the transformation of steroid 17-oximes to the corresponding alkene nitriles regioselectively,[19] pivaloyl chloride/DMF a mild inexpensive and non-toxic system for the conversion of oximes to corresponding amides[20] (**scheme. I.1**), triphosphazene catalyzed Beckmann rearrangement of ketoximes to lactams,[21] mercury-catalyzed rearrangement of ketoximes into amides and lactams,[22] ruthenium-catalyzed oxime to amide rearrangement.[23]



Scheme.I.1. Beckmann rearrangement of oximes using pivaloyl chloride

I.4.3. Application of nitriles in organic transformations

Nitriles are useful precursor for the synthesis of wide range of nitrogen containing heterocyclic compounds. The nitriles are widely used for the preparation of nitrogen containing heterocyclic compounds such as synthesis of pyridine derivatives[24] single-step synthesis of pyrimidine derivatives,[25] synthesis of 3, 5-diaryl-1, 2, 4-thiadiazoles in 1-butyl-3-methylimidazolium bromide promoted by $(NH4)_2S$ and (2, 4, 6-trichloro-1, 3, 5-triazine) TCT–DMSO,[26] synthesis of highly functionalized pyridines by cyclotrimerization of one nitrile with two alkynes in the presence of water-soluble cobalt(I) catalyst in the aqueous media,[27] synthesis of 5-substituted 1*H*-tetrazoles through 1, 3-dipolar cycloaddition of boron-azides and nitriles[28] (**scheme I.2.**), preparation of 2-substituted pyrrolidines from commercially available nitriles,[29] the Ni(0)-catalyzed the synthesis of variety of pyridines by intermolecular dehydrogenative [4 + 2] cycloaddition reaction of 1, 3-butadienes with nitriles,[30] $AgNO_3$ catalyzed synthesis of 5-substituted-1*H*-tetrazole via [3+2] cycloaddition of nitriles and sodium azide in refluxing DMF.[31]



Scheme.I.2. Synthesis of 5-substituted 1*H*-tetrazoles

I.4.4. Application of benzimidazole in organic organic transformations

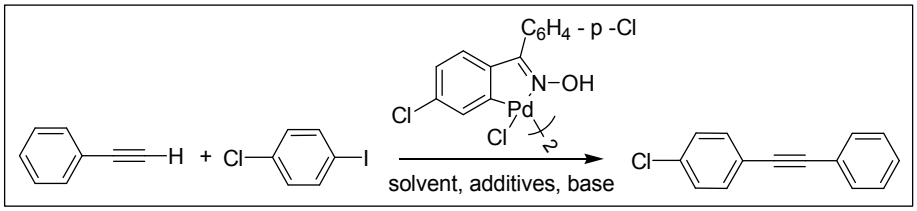
Benzimidazoles are one of versatile compounds having wide application in numerous research areas such as synthesis of tripodal fluorescent receptor bearing benzimidazole motifs as recognition sites in the pods of the receptor which is highly selective fluorescent chemosensor for iodide in aqueous solution,[32] benzimidazole and related ligands for Cu-catalyzed azide-alkyne cycloaddition,[33] hybrid NH_2-benzimidazole ligands for efficient Ru-catalyzed asymmetric hydrogenation of aryl ketones.[34]

I.4.5. Application of imidazoles in organic transformations

As imidazole moiety is associated with many bioactive useful organic compounds, it plays a useful starting material for the synthesis of wide range of nitrogen containing physiologically active natural and synthetic compounds.[35] Due to the presence of two nitrogen atom, the suitable derivatives of the imidazole act as important ligand to many transition metals. Imidazole serves as a useful organic counterpart for the preparation of ionic liquids. Now days, imidazoles is also used as organo-catalyst for considerable organic transformation.

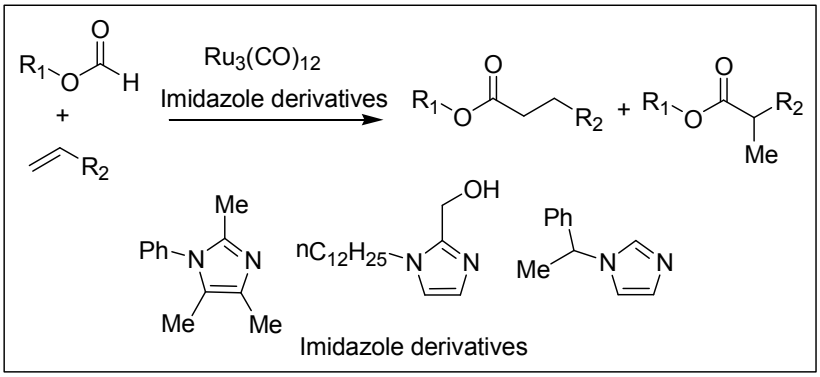
I.5. Role of oximes, benzimidazoles and imidazoles derivatives in organic ligands

Carbon-heteroatom containing organic compounds plays an important role in the development of transition metal coordination chemistry due to their versatile bonding modes. Oximes and their metal complexes are of current interest for their various physicochemical properties, reactivity patterns and potential applications in many important chemical processes in medicine and catalysis. The aryl palladium complexes especially ortho functionalized aryl complexes have the numerous interesting applications in organic synthesis. Catalytic C−C or C−heteroatom coupling reactions are usually carried out in the presence of aryl palladium complexes with nucleophiles. Oxime based palladacycles have gained a special attention in modern organic synthesis due their ubiquitous use in variety of catalytic transformations (**Scheme.I.3.**).[36-40] Literature review revels that benzimidazole and related ligands are also used for the effective ligands in various transformation such as Cu-catalyzed azide-alkyne cycloaddition,[41] hybrid NH_2-benzimidazole ligands for efficient Ru-catalyzed asymmetric hydrogenation of aryl ketones.[42]



Scheme.I.3. Oxime palladacycles catalyzed Sonogashira cross-coupling

Various derivatives of imidazole are used as a useful ligand for considerable number of transition metals. Kei Manabe et al.[43] reported the Ru-catalyzed hydroesterification of alkenes using formates, affording one-carbon elongated esters in high yields using imidazole derivatives as a effective ligand (**scheme.I.4.**). Aaron Aponick et al.[44] reported the design, preparation and implementation of an imidazole-based chiral biaryl P, N-ligand for asymmetric catalysis where the ligand found to perform exceptionally well in the enantioselective coupling. Roman Sívek, Filip Bureš et al.[45] reported the synthesis and application in asymmetric synthesis of imidazole based potential bi-and tridentates ligand.



Scheme.I.4. Ru-catalyzed hydroesterification of alkenes

I.6. Use of imidazole for the preparation of ionic liquid

Imidazole-based ionic liquids have found uses in several applications including potential water treatment agents due to their ability to coordinate with metal atoms, and they are also recognized for their potential as green organic solvents due to their lack of volatility.[46] Furthermore, a unique combination of various alkyl substituents and counteranions enables tuning of the properties of the liquid to meet the demands of the application. The first imidazole based ionic liquid was 1-ethyl-3-methylimidazolium chloride (**fig.I.4.**). Later on anion exchange with more hydrolytically stable anions such as BF_4^-, PF_6^-, NO_3^-,SO_4^-, or acetate that the resulting ionic liquids were quite stable.[47] This development led to the birth of the imidazole-based modern day ionic liquid.

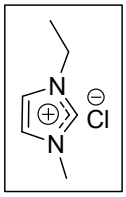
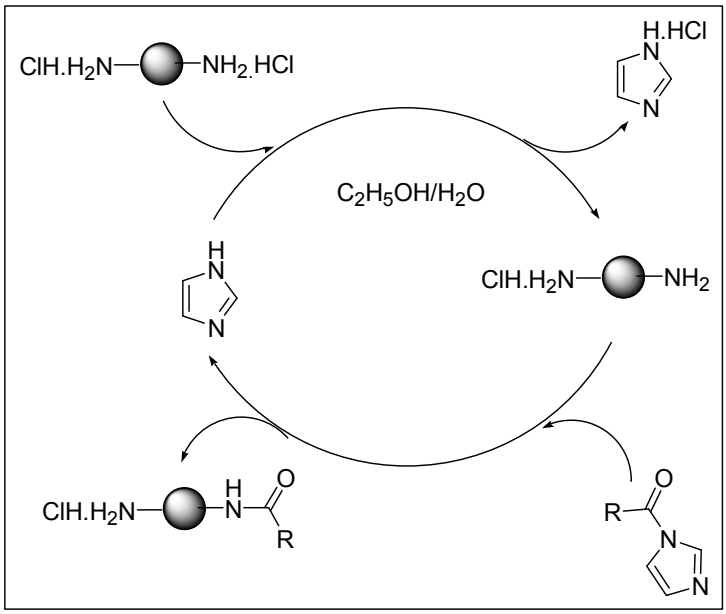


Fig.I.4.1-Ethyl-3-methylimidazolium chloride

I.7. Role of imidazoles and its derivatives in catalysis

Imidazole and imidazole tuned with transition metal shows highly effective catalytic properties for numerious organic transformations. Yasuhiro Uozumi et al.[48] reported self-assembled poly(imidazole-palladium) as highly active reusable catalyst for the allylic arylation/alkenylation of allylic acetates and carbonates with tetraarylborates, arylboronic acid, and alkenyl boron reagents in alcohol and/or water. Later on, the same group again reported the self-assembled copper sulfate and a poly-(imidazole−acrylamide) amphiphile as highly efficient solid phase catalyst for the Huisgen 1, 3-dipolar cycloaddition of a variety of alkynes and organic azides, including the threecomponent cyclization of a variety of alkynes, organic halides, and sodium azide.[49] M. P. Kaushik et al.[50] reported an simple imidazole catalyzed selective monoacylation of symmetrical aliphatic primary and secondary diamine (**scheme.I.5.**).



Scheme.I.5. Imidazole catalyzed selective monoacylation of symmetrical diamine

Marc L. Snapper et al.[51] reported use of an amino acid based imidazole catalyst for the enantioselective catalytic silylation of racemic diols which offers access to enantiomerically enriched monosilylated regioisomers.

I.8. Conclusion

Compounds having carbon-hetero bonds have a broad scope in the area of designing the molecules with a chemical, biological or pharmaceutical interest. Most of the pharmaceuticals are covered by the compounds having carbon-hetero bonds. The bioactive natural products include carbon-heteroatom bond in their functional site. Therefore, molecules having carbon-hetero bond would be the suitable intermediates for natural product synthesis. Chemically interesting suitable molecules having bi or multifunctional system would perform efficient ligands for the complicated organic transformations. Carbon-hetero bond can be more easily functionalize than carbon-carbon non polar olefin bond. Functional groups inter-conversion, preparation of bi-or multifunctional compounds can be easily carry out by applying suitable reagents to carbon-hetero bond. With these huge importance and broad scope of carbon-hetero bond, author felt necessary to find a mild and easiest route for the synthesis of such type of important organic intermediate under mild, easy and straightforward approach.

I.9. References

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CHAPTER-II

Selective epoxidation of steroidal skeleton by *m*-chloroperbenzoic acid (*m*CPBA)

CHAPTER-II

SECTION-A

II.A. A brief review on epoxide, synthesis and its applications

II.A.1. Epoxide (oxirane)

An epoxide is cyclic ether with three ring atoms (**fig.II.A.1.**).These rings approximately define an equilateral triangle, which makes it highly strained. The strained ring makes epoxides more reactive than other ethers. Simple epoxides are named from the parent compound ethylene oxide or oxirane.

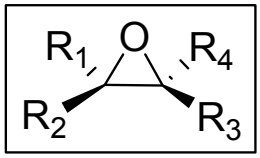


Fig.II.A.1. Epoxide (oxirane)

II.A.2. Natural occurance of epoxide

Organic compounds having oxygenated functions such as aldehydes, alcohols, phenols, carboxylic acids and esters are widely found in nature. The natural occurance of three member cyclic ether is comparatively low. József Deli et al.[1] have recently reported the isolation of new carotenoids, cryptocapsin-5, 6-epoxide, 3'-deoxycapsanthin-5, 6-epoxide, and cryptocapsin-5,8-epoxides, from the ripe fruits of red mamey (Pouteria sapota) (**fig.II.A.2.**).

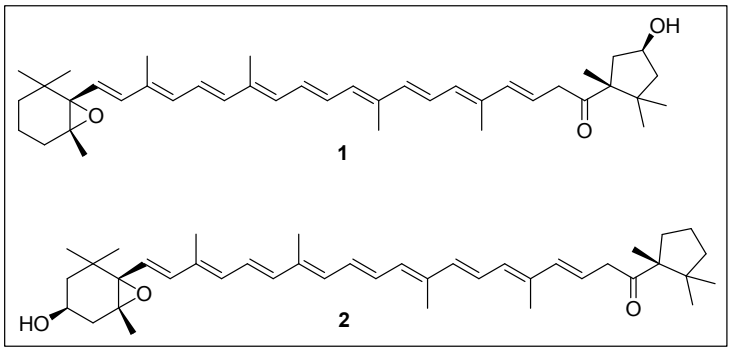
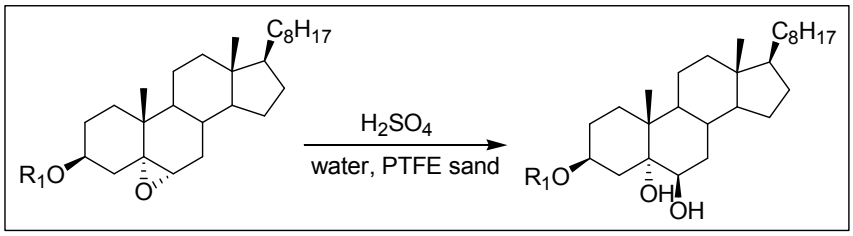


Fig.II.A.2. (5R, 6S)-cryptocapsin-5, 6-epoxide (**1**), 3'Deoxycapsanthin-5, 6-epoxide (**2**)

II.A.3. Application of epoxide in organic transformations

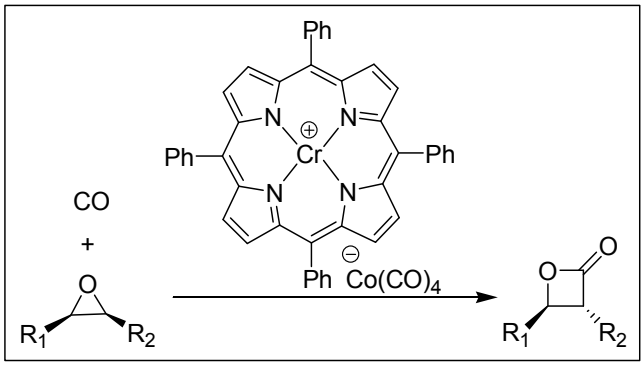
Epoxides are one of the useful precursors for the synthesis of *trans*-diol. It is also useful starting material for the synthesis of various useful organic compounds such as the preparation of dihydroxylated steroids in a quantitative yield by stirring a mixture of a very sparingly soluble high melting steroidal epoxide, polytetrafluoroethylene (PTFE) sand, and aqueous H_2SO_4 without organic solvents or phase transfer catalysts (**scheme.II.1.**).[2]



Scheme.II.A.1. Ring opening of steroidal epoxides

Epoxides are considered as versatile intermediates in organic synthesis, which are susceptible to nucleophilic attack to form the substituted hydroxyl products.[3] Ring opening of epoxides with nucleophilic reagents is an useful tool for the preparation of several 1,2-disubstituted

products.[4] Literature review revealed that substantial amount of organic transformation have been carried out with epoxides such as bifunctional organocatalysts bearing an ammonium betaine framework catalyzed for activation of carbon dioxide and epoxides to produce cyclic carbonates,[5] bimetallic catalyst comprised of a chromium(III) porphyrin cation and a cobalt tetracarbonyl anion catalyzed carbonylation of epoxides to β-lactones (**scheme.II.A.2.**),[6] stereoselective synthesis of pentacyclic steroids from cholic acid, by asymmetric epoxidation and stereoselective intramolecular epoxide opening lactonization,[7] mesoporous aluminosilicates catalyzed ring-opening reactions of epoxides with aromatic amines to produce β-amino alcohols,[8] hydrazine sulphate catalyzed metal-free regioselective ring opening of epoxides with alcohols to afford the corresponding β-alkoxy alcohols including several epoxysteroids, with a wide set of representative alcohols,[9] Lewis acid catalyzed transformation of epoxides to acetonides.[10]



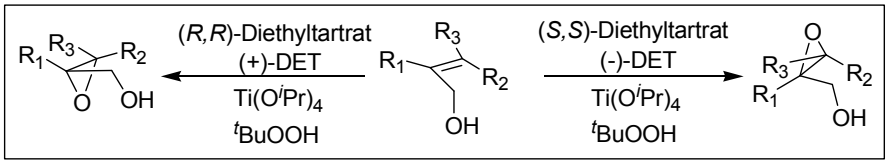
Scheme.II.A.2. Carbonylation of epoxides to β-lactones

II.A.4. Method for the synthesis of epoxide

The dominant epoxides industrially are ethylene oxide and propylene oxide, which are produced respectively on the scales of approximately 15 and 3 million tonnes. The epoxidation of ethylene involves its catalytic reaction with oxygen. The direct reaction of oxygen with alkenes is useful only for this epoxide. Other alkenes fail to react usefully, even propylene. Most epoxides are generated by treating alkenes with peroxide-containing reagents, which donate a single oxygen atom. Typical peroxide reagents include hydrogen peroxide, peroxycarboxylic acids (generated in-situ or preformed), and alkyl hydroperoxides. In specialized applications, other peroxide-containing reagents are employed, such as dimethyldioxirane. The largest scale application of this approach is the production of propylene oxide from propylene using either tert-butyl hydroperoxide or ethylbenzene hydroperoxide.

II.A.4.1. Sharpless epoxidation

In 1980, Sharpless et al.[20] reported the stoichiometric asymmetric epoxidation of allylic alcohols. The Sharpless epoxidation reaction is an enantioselective chemical reaction to prepare 2, 3-epoxyalcohols from primary and secondary allylic alcohols (**scheme.II.A.3.**). The stereochemistry of the resulting epoxide is determined by the diastereomer of the chiral tartrate diester (usually diethyl tartrate or diisopropyl tartrate) employed in the reaction. The oxidizing agent is *tert*-butyl hydroperoxide. Enantioselectivity is achieved by a catalyst formed from titanium tetra(isopropoxide) and diethyl tartrate. Only 5–10 mol% of the catalyst in the presence of 3Å molecular sieves is necessary.

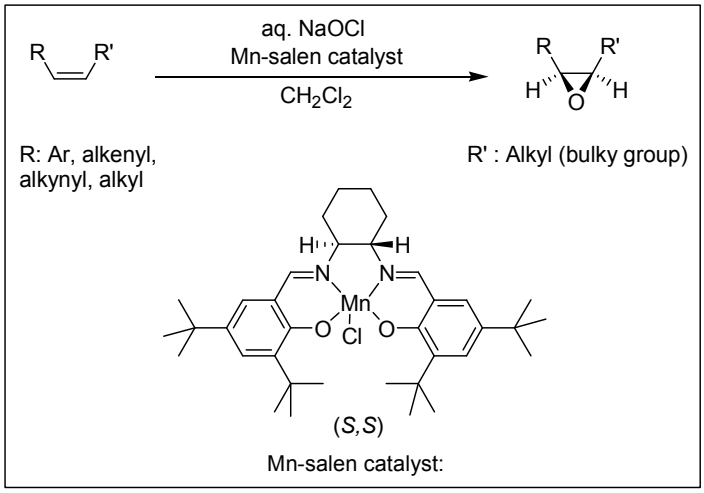


Scheme.II.A.3. Sharpless asymmetric epoxidation

The Sharpless epoxidation's success is due to five major reasons. First, epoxides can be easily converted into diols, aminoalcohols or ethers, so formation of chiral epoxides is a very important step in the synthesis of natural products. Second, the Sharpless epoxidation reacts with many primary and secondary allylic alcohols. Third, the products of the Sharpless epoxidation frequently have enantiomeric excesses above 90%. Fourth, the products of the Sharpless epoxidation are predictable using the Sharpless Epoxidation model. Finally, the reactants for the Sharpless epoxidation are commercially available and relatively cheap.

II.A.4.2. Jacobsen Epoxidation

The Jacobsen epoxidation allows the enantioselective formation of epoxides from various *cis*-substituted olefins by using a chiral Mn-salen catalyst and a stoichiometric oxidant (**scheme.II.A.4.**).[21-22] Compared to the Sharpless epoxidation, the Jacobsen epoxidation allows a broader substrate scope for the transformation: good substrates are conjugated *cis*-olefins (R: Ar, alkenyl, alkynyl; R': Me, alkyl) or alkyl-substituted *cis*-olefins bearing one bulky alkyl group.



Scheme.II.A.4. Mn-salen catalyzed epoxidation of cis olefin

II.A.4.3. Miscellaneous methods for the preparation of epoxides

Joan Selverstone Valentine et al.[23] have reported Lewis acid ferric complex, $(Et_3HN)Fe^{III}(bpb)Cl_2$ (**fig.II.A.3.**) and its triflate derivatives $(Et_3HN)Fe^{III}(bpb)(OTf)_2$ catalyzed epoxidation of a variety of olefins by iodosylbenzene, OIPh.

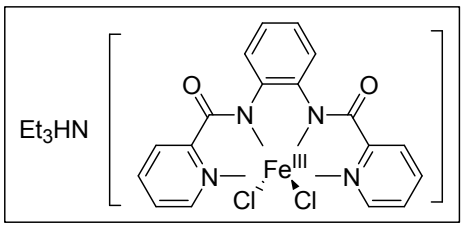
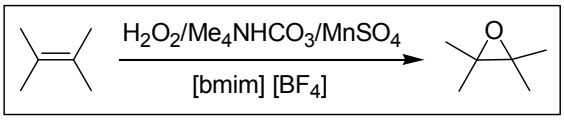


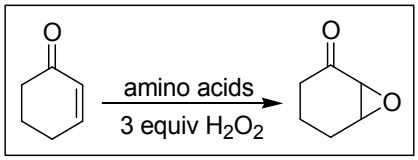
Fig.II.A.3. $(Et_3HN)Fe^{III}(bpb)Cl_2$

Literature review revealed that numerous catalytic system and substantial numbers of oxidant have been employed for the preparation of epoxide from olefins such as fructose-derived ketone catalyzed asymmetric epoxidation of olefins by oxone,[24] enantioselective epoxidation of *cis*-olefins by chiral dioxirane,[25-26] epoxidation of electron-deficient olefins with a cationic manganese complex,[27] pentafluorophenyl Pt^{II} Complexes catalyzed asymmetric epoxidation of terminal alkenes with hydrogen peroxide,[28] organocatalytic asymmetric epoxidation of α, β-unsaturated aldehydes using a sterically encumbered chiral pyrrolidine derivative and hydrogen peroxide as the oxidant,[29] iron-catalyzed asymmetric epoxidation of acyclic β, β-disubstituted enones,[30]

tungsten-catalyzed asymmetric epoxidation of allylic and homoallylic alcohols with hydrogen peroxide,[31] epoxidation of lipophilic alkenes using hydrogen peroxide was accomplished with the manganese sulfate/bicarbonate catalytic system in an ionic liquid at room temperature (**scheme.II.A.5**),[32] amino-acid-mediated epoxidation of α,β-unsaturated ketones by hydrogen peroxide in aqueous media (**scheme.II.A.6.**).[33]



Scheme.II.A.5. Epoxidation of lipophilic alkenes using hydrogen peroxide



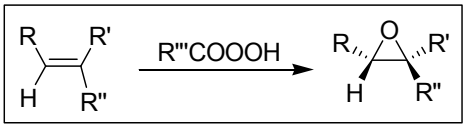
Scheme.II.A.6. Amino-acid-mediated epoxidation of α,β-unsaturated ketones

II.A.5. Epoxidation by peroxy acids

m-Chloroperoxybenzoic acid (*m*CPBA) is a peroxycarboxylic acid used widely as an oxidant in organic synthesis. *m*CPBA is often preferred to other peroxy acids because of its relative ease of handling. The main areas of use are the conversion of ketones to esters (Baeyer-Villiger oxidation), epoxidation of alkenes (Prilezhaev reaction), conversion of silyl enol ethers to silyl α-hydroxy ketones (Rubottom oxidation), oxidation of sulfides to sulfoxides and sulfones, and oxidation of amines to produce amine oxides.

II.A.5.1. Prilezhaev reaction

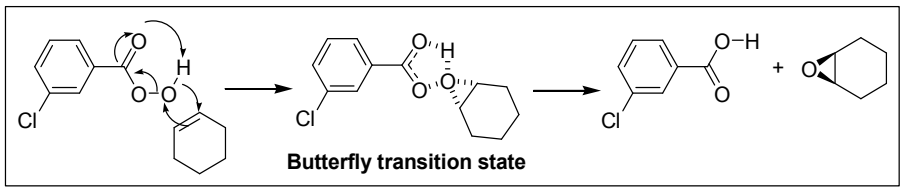
This reaction involves the reaction of peracids and alkenes to give oxiranes. The commercial available *m*CPBA is a widely used reagent for this conversion, while magnesium mono-perphthalate and peracetic acid are also employed (**scheme.II.A.7.**).



Scheme.II.A.7. Epoxidation of olefin by peracid

II.A.5.2. Mechanism of the Prilezhaev reaction

Peracids tend to adopt an intramolecularly hydrogen-bonded conformation in solution, and the high degree of polarisation results in an electrophilic oxygen atom that is able to add to alkenes.The transition state, in which oxygen is added and the proton is shifted simultaneously, resembles a butterfly and is known as the "Butterfly Mechanism."



II.A.6. Conclusion

As epoxide is versatile organic intermediate for preparation of 1,2-disubstituted compounds. The literature review reveals that there no sufficient literature report for the selective and green methods for the preparation of epoxide derivatives. Because of ample applications of epoxide in organic transformations, author felt necessary to develop an easy and green pathway for the epoxidation reaction.

II.A.7. References

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CHAPTER-II

SECTION – B

Selective epoxidation of steroidal skeleton by *m*-chloroperbenzoic acid (*m*CPBA)

II.B. Present Investigation

II.B.1. Background of the present investigation

Epoxidation of double bond has proved to be one of the most useful reactions in organic synthesis, since it provides important intermediate for the synthesis of wide range of compounds with chemical and biological interest.[1] Ring opening of epoxides with nucleophilic reagents is an useful tool for the preparation of several 1, 2-disubstituted products such as preparation of dihydroxylated derivatives in a quantitative yield,[2] preparation of β-lactone,[3] activation of carbon dioxide and epoxides to produce cyclic carbonates,[4] synthesis of β-amino alcohols,[5] preparation of β-alkoxy alcohols,[6] transformation of epoxides to acetonides[7-12] and it is very useful starting material for many valueable transformative reactions.[13-19] Epoxidation of olefins could be carried out with various catalytic systems, in which complexes of ruthenium,[20] manganese,[21] polyoxometalates,[22] and oxovanadium Schiff base[23] could all be used as catalysts.

It is well documented that *m*CPBA is known to be very useful for the oxidation and rearrangement of various types of natural and synthetic substances.[24-30] Literature review revealed that there are a few reports of reaction of steroidal skeletons with *m*CPBA.[31-32] However, to the best of our knowledge, the selective epoxidation of steroidal skeleton by *m*CPBA under solvent-free condition has not been reported so far. Although a substantial synthetic strategies have been developed for the epoxidation of olefinic bonds, the use of expensive catalyst, hazardous metal salts, work-up difficulties made the various existing methodologies non desirable under the aspect of sustainable synthesis. Because of wide application of epoxides as starting material for designing the molecules with biological and pharmaceutical interest, there is demand for less expensive, straightforward and environmentally friendly protocols for their synthesis. Therefore, the development of environmentally benign and selective epoxidation

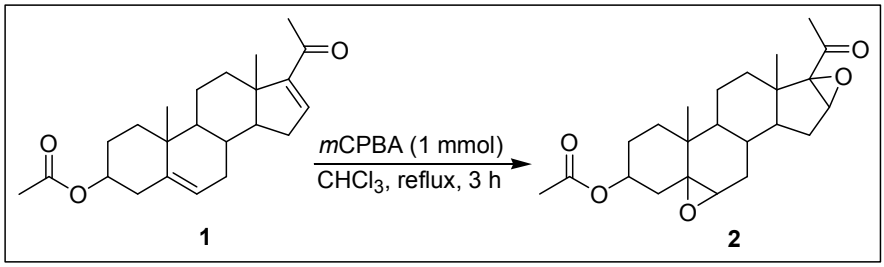
methods under mild conditions is an important research topic because epoxy compounds are widely used as intermediates to obtain value-added chemical products.

With these backgrounds of *m*CPBA and application of epoxides, our investigation were to search for a milder reaction condition coupled with use of environment-friendly, cost efficient, high functional group tolerance and high yielding protocol for the epoxidation of steroidal skeleton.

In recent years, silica gel have attracted intensive interest for their being a possible replacement of traditional solvents for organic synthesis, particularly in the area of green chemistry, due to their advantageous properties, including non toxic medium for organic reactions, high thermal and chemical stability. For the development of easy and clean procedures for obtaining steroidal epoxy derivatives, herein we report a new methodology for the selective synthesis of steroidal epoxides of 16-dehydropregnenolone, β-sitosterol and the derivatives of β-sitosterol and cholesterol using *m*CPBA in silica at room temperature under solvent free condition.

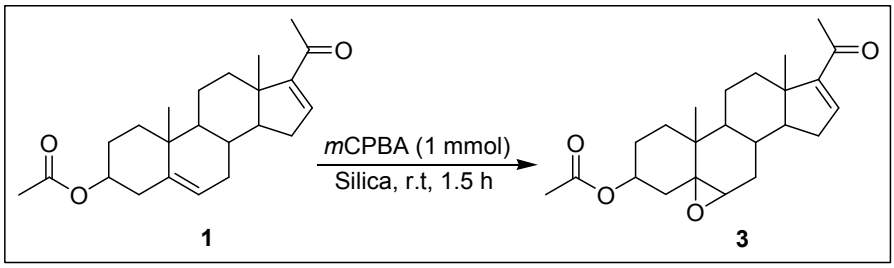
II.B.2. Results and discussion

In an endeavour to start our present investigation we have chosen 16-dehydropregnenolone acetate (16-DPA) as our model compound for desired transformation. As 16-DPA has two carbon-carbon double bonds, one is at 5, 6-position (less polar double bond) and another is at 16, 17-position (more polar double bond) and we thought it may be an interesting candidate for the epoxidation reaction with *m*CPBA. Initially, we started our investigation by taking 16-DPA (0.5 mmol) and *m*CPBA (1 mmol) in chloroform and allow them to react at room temperature. Only a weak spot of product was appeared in TLC after 5 h. We repeated the same reaction under reflux condition by expecting simultaneous 5, 6-epoxidation and Bayer-Villeger type of oxidation in an enone part. After 3 h, the reactant disappeared from the reaction mixture which was confirmed by TLC. The isolated product were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy and elemental analysis and found isomeric mixture of 5, 6-16, 17-diepoxy derivative of 16-dehydropregnenolone (**2**) in 93.54 % isolated yield (**scheme.II.B.1.**).



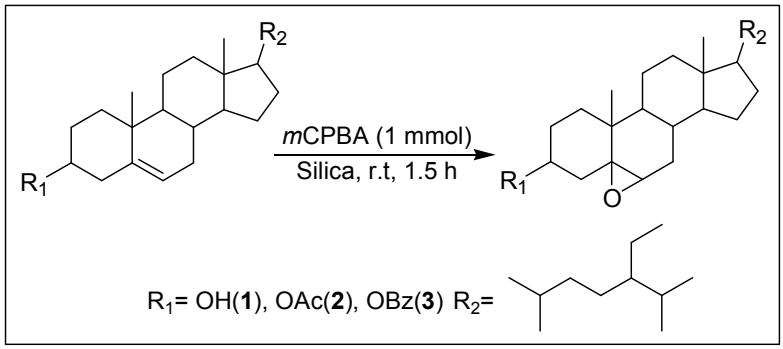
Scheme.II.B.1. Epoxidation of 16-DPA in chloroform

The same reaction was performed on activated silica (silica gel 60-120 mesh) by grinding the 16-DPA (0.5 mmol) and *m*CPBA (1 mmol) and allowing the mixture to stir at room temperature under solvent free condition. After 1.5 h, the reactant disappeared from reaction mixture which was confirmed by TLC. Interestingly, TLC spot of the product were different from the reaction which was performed in chloroform. Finally, after purification and characterization of the product by IR, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy and elemental analysis, we found selective epoxidation of 16-DPA at 5,6-position to furnish 5, 6-epoxy derivative of 16-DPA (**3**) in 91.54 % isolated yield (**scheme.II.B.2**).



Scheme.II.B.2. Selective epoxidation of 16-DPA on silica under solvent free condition

With this interesting selectivity and encouraging yield, we extended our interest towards β-sitosterol, β-sitosterol acetate, β-sitosterol benzoate and cholesterol acetate, cholesterol benzoate (**scheme.II.B.3.**). The reactions were performed on silica at room temperature under solvent free condition. These steroids and their derivatives also furnished very good result (**table.II.B.1.**).



Scheme.II.B.3. Epoxidation steroids on silica under solvent free condition

Table.II.B.1.

Epoxidation of steroids on silica under solvent free condition

Entry	Substrate	Time (h)	Yield (%)[b]
1	β-sitosterol	1.5	88
2	β-sitosterol-3-acetate	1.5	86
3	β-sitosterol-3-benzoate	1.5	82

II.B.3. Experimental

II.B.3.1. Chemicals

All the chemicals which were used for the present investigation are listed in the **table.II.B.2.** The details of the chemicals regarding their source and purity are summarised in **table.II.B.2.**

Table.II.B.2.

Chemicals used for the present investigation

Entry	Chemical	Source	Purity (%)
1	β-sitosterol	ACROS	75
2	*m*Chloroperbenzoic acid	ACROS	70-75
3	Acetic anhydride	Thomas Baker	99
4	Benzoyl chloride	LOBA Chemie	99
5	Sodium sulphate anhydrous	SRL	99.5
6	Sodium bicarbonate	SRL	99.7
7	Chloroform	RFCL	99

8	Ethyl acetate	Thomas Baker	99
9	Petrolium ether	Thomas Baker	99
10	Potassium bromide for FT IR	Merck	99
11	$CDCl_3$ for NMR	ACROS	99.8
12	Silica gel 60-120 mesh for column	SRL	-
13	Silica gel for TLC	SRL	-

II.B.3.2. Reaction procedure and purification

II.B.3.2.1. Preparation of 16-dehydropregnenolone acetate (16-DPA)

16-DPA was prepared from a steroidal saponin diosgenin obtained by extraction from naturally occurring Dioscorea Floribunda (collected from Research and development laboratories, Directorate of Cinchona and other medicinal plants, Mungpoo, Darjeeling, West Bengal, India). Acylation of diosgenin was carried out by taking diosgenin (5 g, 0.012 mol), acetic anhydride (4 mL, 0.04 mol) and xylene (15 mL) in an autoclave at 250 ^{o}C for 10 h. After completion of reaction, the reaction mixture was allowed to cool at room temperature. The solvent was evaporated by rotary evaporator to obtain pseudo diosgenin diacetate (solid mass) having melting point 98 ^{o}C (lit,[33] 97-98 ^{o}C). Pseudo diosgenin diacetate was further oxidised by aqueous acidic solution of chromium trioxide [CrO_3 (0.5 mol), H_2O (5mL), CH_3COOH (2mL)] at (0-5 ^{o}C) by dropwise addition of oxidant to an ice cold solution of pseudo diosgenin diacetate (5g) in dichloromethane (10 mL), glacial acetic acid (10 mL) and water (2.5 mL). After complete addition of oxidant, the temperature of reaction mixture was raise to 15 ^{o}C and stirred for 25 minutes. Sodium chloride (0.5 g in 20 mL H_2O) and methanol (1 mL) were added to reaction mixture and stirred for 20 minutes. Extraction of organic layer followed by column chromatography furnished pure diosone. The obtained diosone was hydrolysed by glacial acetic acid for 2 h. The reaction mixture was extracted followed by distillation and recrystallised to obtained creamy coloured 16-DPA of Mp 172 ^{o}C (lit,[34] 172-173 ^{o}C)

II.B.3.2.2. Epoxidation of 16-DPA, β-sitosterol and its derivatives by *m*CPBA on silica

Solid support (silica gel 60-120 mesh, 1gm per 0.5 mmol of substrate) was activated by heating (80 ^{o}C) in a laboratory oven for 2 h. The activated silica was then cooled to

room temperature. Starting material (steroid) (0.5 mmol) and *m*CPBA (1 mmol) were then mixed intimately with activated silica in mortor and pestle. The reaction mixture was magnetically stirred at room temperature for 1.5 h. Completion of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was extracted with $CHCl_3$ (100 ml), washed with 10% $NaHCO_3$ solution (3x50 ml) followed by washing with water and dried over anhydrous Na_2SO_4 (1 g) and chromatographed over a column of silica gel to furnish epoxy steroid in pet ether-ethyl acetate (94:6) eluent.

II.B.3.2.3. Epoxidation of 16-DPA by *m*CPBA in chloroform

16-dehydropregnenolone (16-DPA) (0.5 mmol) was dissolved in distilled chloroform (15 ml). *m*CPBA (1 mmol) was added in small lots with continuous shaking. The reaction mixture was then refluxed for 3 h. Completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was extracted with $CHCl_3$ (100 ml), washed with 10% $NaHCO_3$ solution (3x50 ml) and washed with water. The combined chloroform extract was dried over Na_2SO_4 and concentrated and chromatographed over a column of silica gel (8 g) to furnish diepoxy derivative of 16-DPA in pet ether-ethyl acetate (93:7) eluent.

II.B.3.2.4. Preparation of β-sitosterol-3-acetate

β-sitosterol (1 mmol) was dissolved in distilled chloroform (10 ml). Acetic anhydride (1.5 mmol) was added drop-wise to the reaction with continuous shaking. The reaction mixture was then warm on oil bath for 3 h. Completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was extracted with $CHCl_3$ (100 ml) and washed with water. The combined chloroform extract was dried over Na_2SO_4 and concentrated and purified by column chromatography to yield pure β-sitosterol-3-acetate and characterized by FT IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

II.B.3.2.5. Preparation of β-sitosterol-3-benzoate

β-sitosterol (1 mmol) was dissolved in distilled chloroform (10 ml) and allowed to stir on a magnetic stirrer. Benzoyl chloride (1.5 mmol) was added drop-wise to the reaction. The reaction mixture was then allowed to stirrer at room temperature for 4 h. Completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was extracted with $CHCl_3$ (100 ml) and washed with water. The

combined chloroform extract was dried over Na_2SO_4 and concentrated and purified by column chromatography to yield pure β-sitosterol-3-benzoate and characterized by FT IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

II.B.3.3. Spectroscopic measurements

IR spectra were recorded in KBr and nujol on Shimadzu FT-IR 8300 Spectrometer. ^{1}H-NMR spectra were recorded on a 300 MHz Bruker Avance FT-NMR spectrometer using TMS as the internal standard, Mass spectra were recorded on a JEOL-AccuTOF JMS-T100LC Mass Spectrometer.

II.B.4. Conclusion

In conclusion, we have developed an easy route to epoxidation of steroids by *m*CPBA on silica at room temperature under solvent free condition. High selectivity, excellent yield, cost efficient, environmental benign, simple work-up process are the major advantages of this protocol. Our investigation will be useful for the preparation of bi- and multi-functional derivatives of steroids.

II.B.5. Characterization data

II.B.5.1. 16-DPA-5, 6-16, 17-diepoxide

Mp 178.2 ^{o}C, white crystalline solid. Found: C, 71.1%; H, 8.31%; O, 20.62%. Calculated for $C_{23}H_{32}O_5$ (388.256): C, 71.08%; H, 8.30%; O, 20.60%. IR (cm^{-1}, KBr): 2925, 1726, 1701, 1560, 1245, 1035, 852. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 4.9-5.0 (m, 1H, H-3), 2.89-2.92 (m, 1H, H-6), 3.66 (d, 1H, J=8.1Hz, H-16) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 15.8, 20, 21.1, 21.3, 27.1, 27.3, 27.4, 27.5, 30.9, 31.3, 31.9, 32, 35.2, 36, 36.6, 37.9, 45, 45.5, 51.2, 58.7 (C-6), 60.4 and 60.2 (C-16), 62.6, 65.2 (C-5), 70.77, 71.24 and 71.18 (C-17), 170.54 and 170.22 (C=O, two isomeric C-3 acetate) 204.91 and 204.75 (C=O, two isomeric C-20) ppm. MS: $[M+1]^+$, *m/z* 389 and $[M+2]^+$, *m/z* 390. Other characteristic peaks appeared at m/z 371, 372, 346, 347.

II.B.5.2. 16-DPA-5, 6-epoxide

Mp 168.5 ^{o}C, white crystalline solid. Found: C, 74.16%; H, 8.69%; O, 17.18%. Calculated for $C_{23}H_{32}O_4$ (372.256): C, 74.14%; H, 8.66%; O, 17.19%. IR (cm^{-1}, KBr): 2943, 1733, 1701, 1660, 1585, 1245, 1039, 869. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.87,

1.11, 2.01, 2.24 (4s, 4 -CH_3 groups), 2.89-2.92 (m, 1H, H-6), 4.9-5.0 (m, 1H, H-3), 6.67 (s, 1H, H-16) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 15.7, 20.3, 21.3, 27.1, 27.2, 28.4, 32, 34.2, 35.2, 36.1, 38, 42.6, 46.1, 51.4, 56.2, 58.7 (C-6), 65.3 (C-5), 71.3, 76.61, 143.99 (C-16), 155.25 (C-17), 170.19 (C=O, acetate C-3), 196.69 (C=O, C-20) ppm. MS: [M^+] *m*/*z*, 372, $C_{23}H_{32}O_4$, other characteristic peaks appeared at *m/z* 313, 270.

II.B.5.3. β-sitosterol-5, 6-epoxide

White crystalline solid. Found: C, 80.86 %; H, 11.71 %; O, 7.42 %. Calculated for $C_{29}H_{50}O_2$ (430.7): C, 80.85 %; H, 11.72 %; O, 7.41 %. IR (cm^{-1}, KBr): 3394, 1156, 964, 722. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.61, 0.82, 0.84, 0.87, 0.91, 1.05, (6s, 6-Methyl groups), 2.89-2.91 (d, 2H, J=6 Hz, H-7), 3.89-3.93 (m, 1H, H-3), ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ,18.7, 19, 19.8, 20.6, 23, 24, 26.1, 28.1, 28.8, 29.1, 29.9, 31, 32.4, 33.9, 34.8, 36.1, 39.4, 39.8, 42.3, 42.5, 45.8, 55.8, 56.8, 59.3 (C-3), 65.8 (C-6), 68.6 (C-5) ppm.

II.B.5.4. β-sitosterol acetate-5, 6-epoxide

White crystalline solid. Found: C, 78.75 %; H, 11.04 %; O, 10.13 %. Calculated for $C_{31}H_{52}O_3$ (472.7): C, 78.76 %; H, 11.08 %; O, 10.14 %. IR (cm^{-1}, KBr): 1734, 1243, 1034, 722. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.61, 0.79, 0.84, 0.88, 0.90, 1.07 (6s, 6-Methyl groups), 2.01 (s, 3-Acetate methyl group) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 19, 19.8, 20.6, 21.3, 23, 24, 26.1, 27.2, 28.1, 28.7, 29.1, 29.7, 29.8, 32.1, 32.4, 33.9, 35, 36.1, 39.3, 42.3, 42.5, 45.8, 55.7, 56.7, 59.1 (C-3), 65.2 (C-6), 71.4 (C-5), 170.2 (C=O, acetate) ppm.

II.B.5.5. β-sitosterol benzoate-5, 6-epoxide

White crystalline. Found: C, 80.83 %; H, 10.16 %; O, 8.96 %. Calculated for $C_{36}H_{54}O_3$ (534.8): C, 80.85 %; H, 10.18 %; O, 8.97 %. IR (cm^{-1}, nujol): 1715, 1279, 1117, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.62, 0.82, 0.84, 0.89, 0.91, 1.12 (6s, 6-Methyl groups), 2.92-2.93 (d, 2H, J=3 Hz, H-7) 5.21-5.22 (m, 1H, H-3), 7.39-7.44 (m, 2H,-Ar), 7.51-7.56 (m, 1H, -Ar), 8.01-8.03 (d, 2H, J=6 Hz, -Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 18.7, 19, 19.8, 20.6, 23, 24, 26.1, 27.3, 28.1, 28.7, 29.1, 29.9, 32.2, 33.9, 35, 36.1, 36.2, 39.3, 42.3, 42.4, 45.8, 55.7, 56.8, 59.2 (C-3), 65.2 (C-6), 72 (C-5), 128.2 (-Ar), 129.5 (-Ar), 130.7 (-Ar), 132.7 (-Ar), 165.7 (C=O, benzoate) ppm

II.B.5.6. β-sitosterol acetate

Mp 132 ^{o}C, White crystal. IR (cm^{-1}, nujol): 1729, 1458, 1375, 1262, 1036, 795. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.65, 0.82, 0.84, 0.91, 0.93, 1.02 (6s, 6-Methyl groups), 2.03 (s, 3-Acetate methyl group), 2.33-2.30 (d, 1H, J=9 Hz, H-7), 4.62 (m, 1H, H-3), 5.38 (s, 1H, H-6) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 19, 19.3, 19.8, 21, 21.4, 23, 24.3, 26, 27.7, 28.2, 29.1, 31.9, 33.9, 36.1, 36.6, 37, 38.1, 39.7, 42.3, 45.8, 50, 56, 56.7, 74, 122.6 (C-6, double bond), 139.6 (C-5, double bond), 170 (C=O) ppm.

II.B.5.7. β-sitosterol benzoate

White solid. IR (cm^{-1}, nujol): 1713, 1373, 1276, 1114, 687. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.68, 0.85, 0.87, 0.91, 0.93, 1.06 (6s, 6-Methyl groups), 2.45-2.47 (d, 2H, J=6 Hz, H-7), 4.84-4.87 (m, 1H, H-3), 5.42 (s, H-6), 7.39-7.44 (m, 2H,-Ar), 7.51-7.55 (m, 1H, -Ar), 8.02-8.05 (d, 2H, J=9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 22.8, 23.8, 24.2, 27.8, 28, 28.2, 31.8, 31.9, 35.8, 36.2, 36.6, 37, 38.2, 39.5, 39.7, 42.3, 50, 56.1, 56.6, 74.5, 122.7 (C-6), 128.2 (-Ar), 129.5(-Ar), 130.8(-Ar), 132.6(-Ar), 139.6 (C-5), 165.9 (C=O, benzoate) ppm.

II.B.6. Supporting spectra

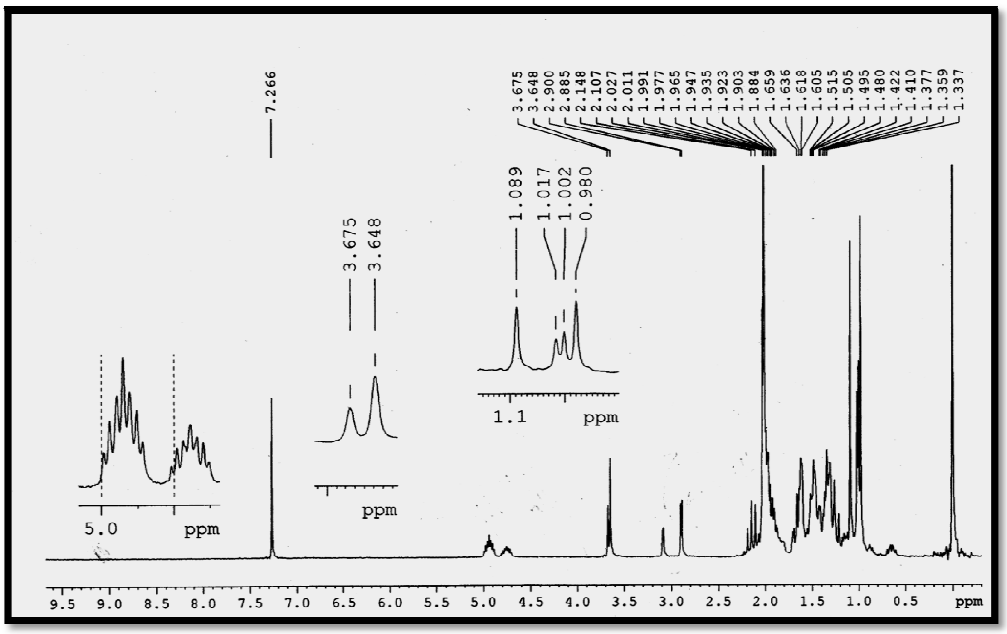


Fig.II.B.1. ^{1}H NMR spectrum of 16-DPA-5,6-16,17-diepoxide

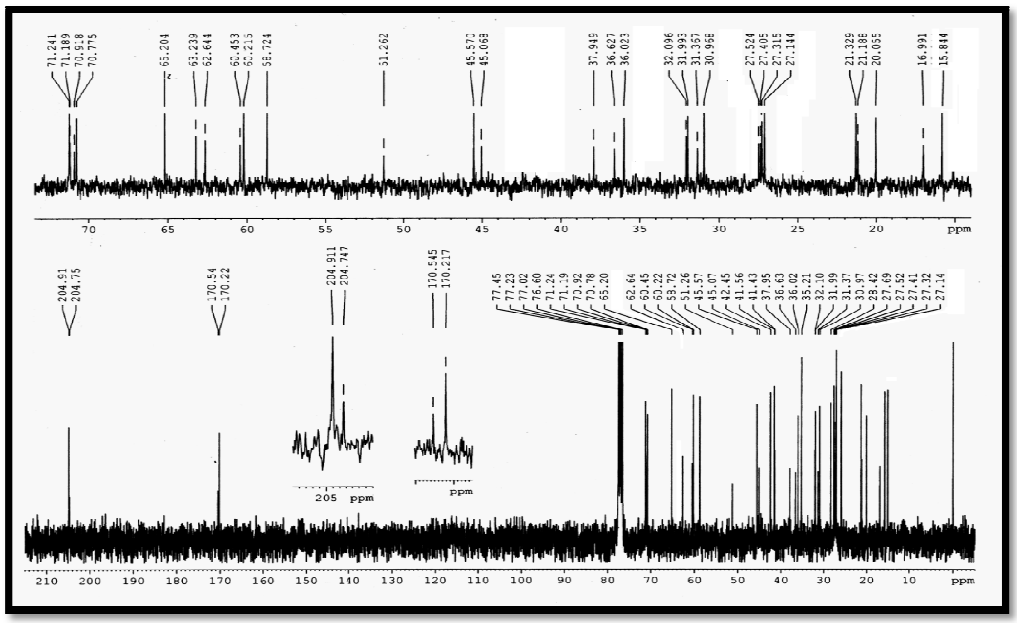


Fig.II.B.2. ^{13}C NMR spectrum of 16-DPA-5,6-16,17-diepoxide

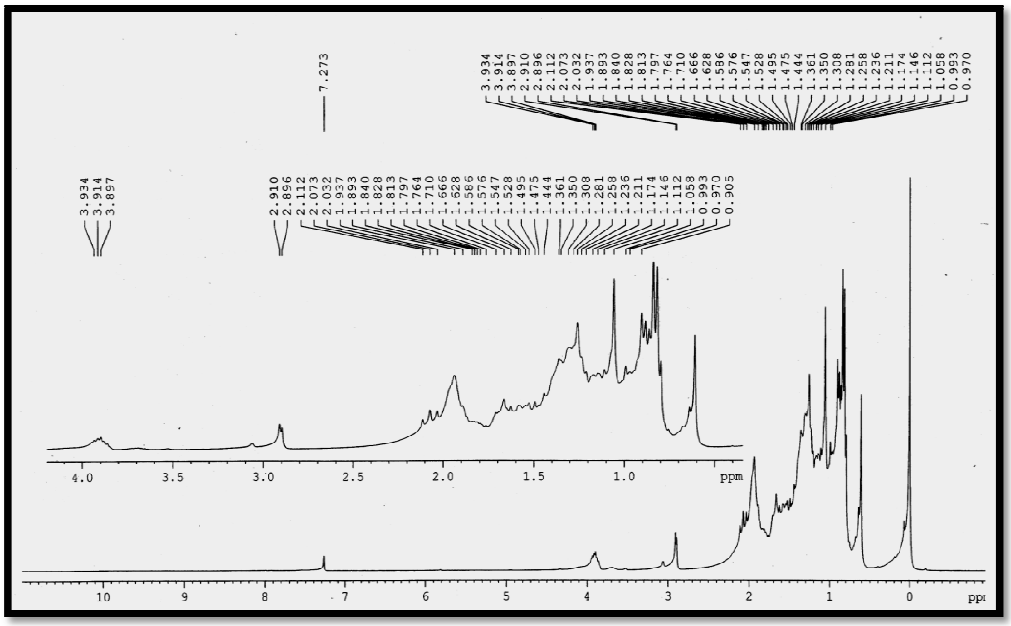


Fig.II.B.3. ^{1}H NMR spectrum of β-sitosterol-5,6-epoxide

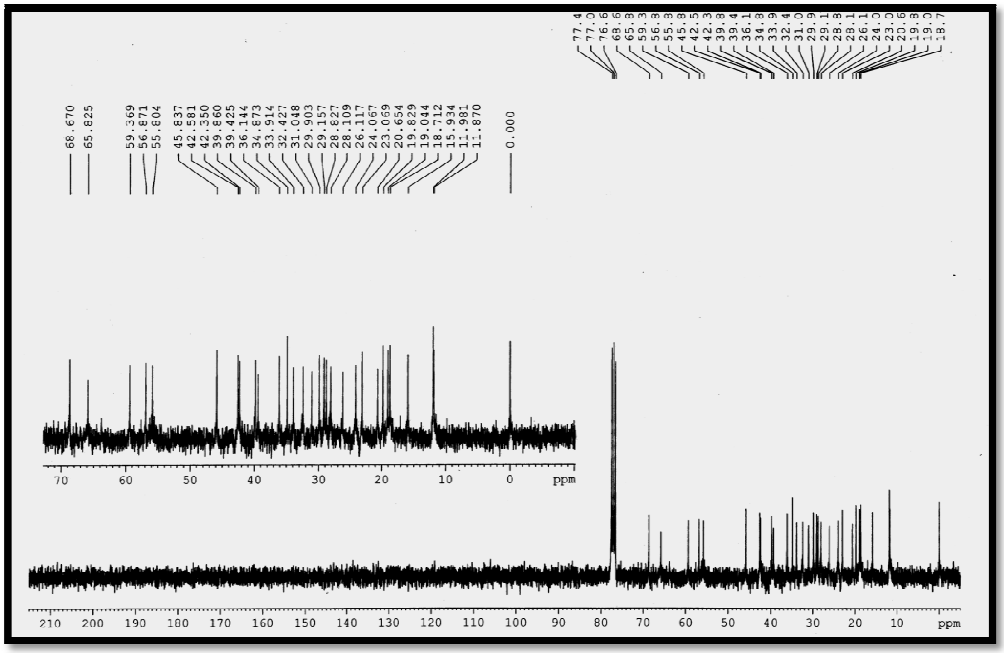


Fig.II.B.4. ^{13}C NMR spectrum of β-sitosterol-5,6-epoxide

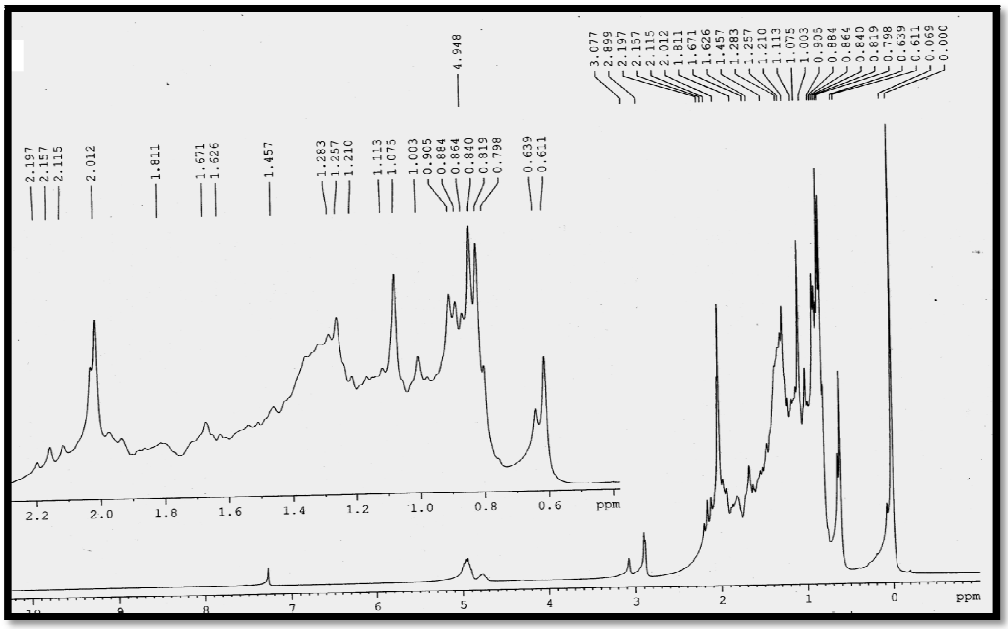


Fig.II.B.5. ^{1}H NMR spectrum of β-sitosterol acetate-5,6-epoxide

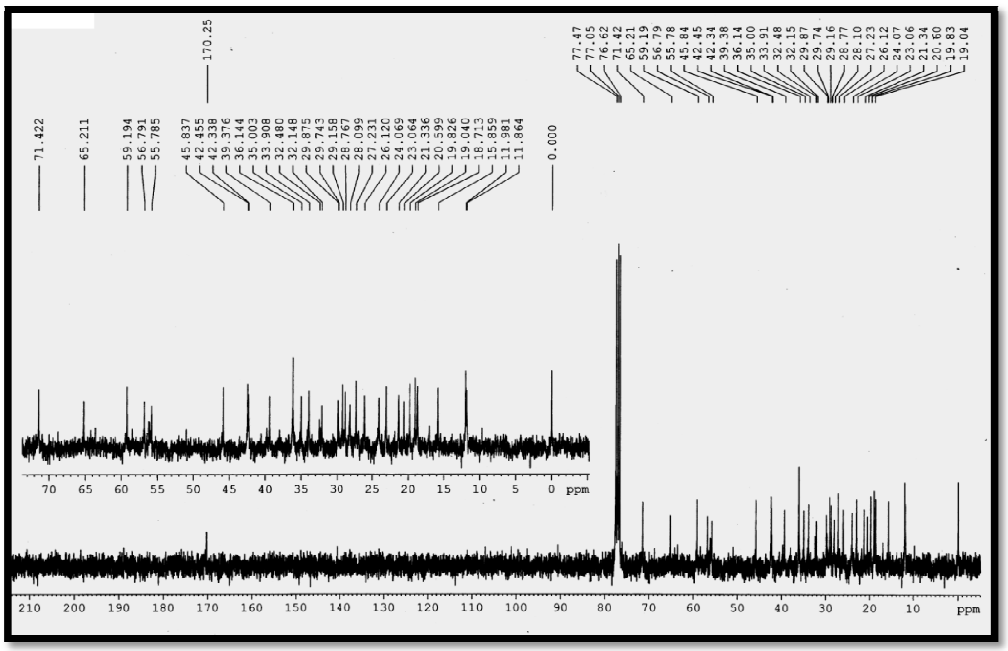


Fig.II.B.6. ^{13}C NMR spectrum of β-sitosterol acetate-5,6-epoxide

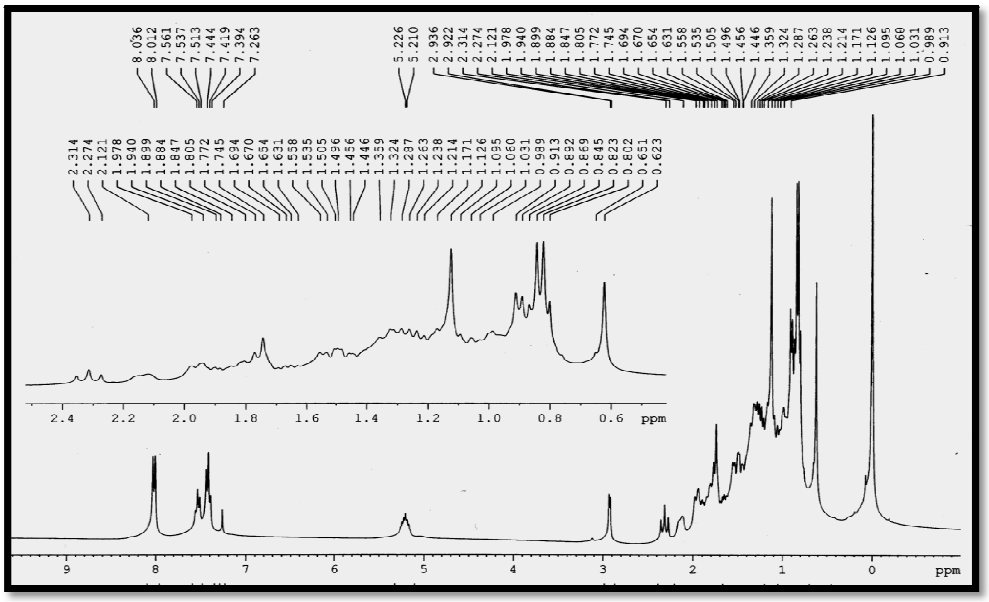


Fig.II.B.7. ^{1}H NMR spectrum of β-sitosterol benzoate-5,6-epoxide

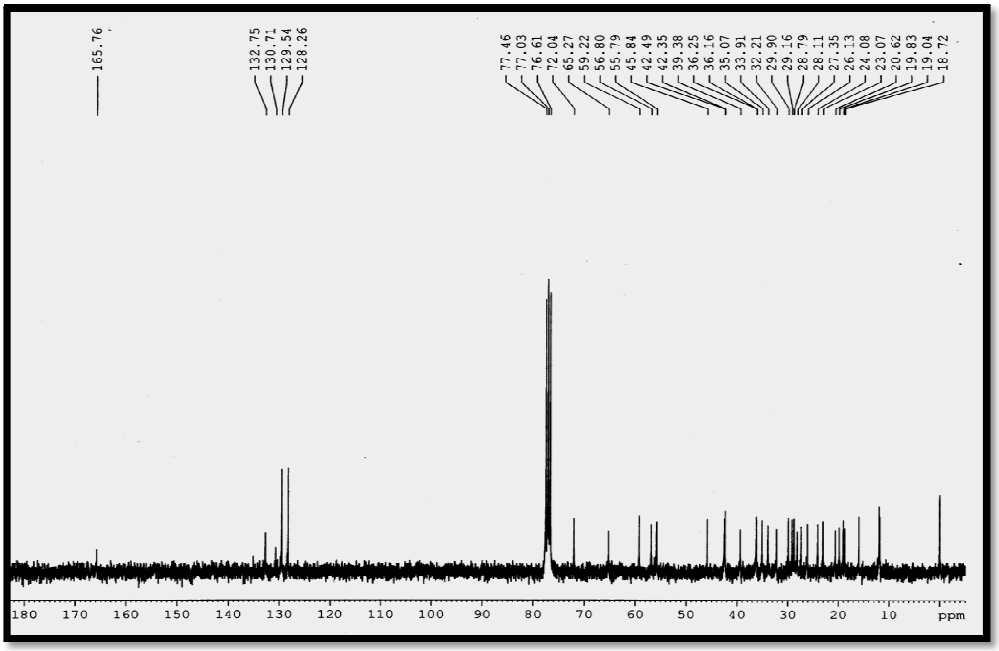


Fig.II.B.8. ^{1}H NMR spectrum of β-sitosterol benzoate-5,6-epoxide

II.B.7. References

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CHAPTER-III

Solid phase synthesis of oxime derivatives

CHAPTER-III

SECTION-A

III.A. A brief review on oxime, synthesis and its applications

III.A.1.1. Oxime

An oxime is a chemical compound belonging to the imines, with the general formula $R_1R_2C=NOH$, where R_1 is an organic side-chain and R_2 may be hydrogen, forming an aldoxime, or another organic group, forming a ketoxime (**fig.III.A.1.**). O-substituted oximes form a closely related family of compounds.

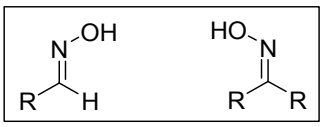


Fig.III.A.1. Example of aldoxime and ketoxime

Oximes are stable and highly crystalline materials and oximation is very efficient method for protection, characterization and purification of carbonyl compounds. These compounds not only represent a useful series of derivatives of carbonyl compounds but also may be used as intermediates for the preparation of wide spectrum of organic compounds and numerous functional group transformations. Among other synthesis applications, these compounds were successfully transformed into number of functional groups and nitrogen containing heterocyclic compounds in the presence of other reacting species. Recently oximes and their derivatives have drawn attention in medicinal research because of their significant bioactivity. In inorganic chemistry, oximes act as a versatile ligand. The Beckmann rearrangement of cyclohexanone oxime to ε-caprolactum is an industrially important reaction for the synthesis of Nylon-6. Moreover, oximes can be easily reduced to amines, which are further used in the manufacturing of dyes, plastics, synthetic fibres and pharmaceuticals. Oximes are used as anti-skinning agents in paint and blocking agents in the polymer industry.

III.A.1.2. Structure of oxime

Oximes exist as two geometric stereoisomers: a syn isomer and an anti isomer. Aldoximes, except for aromatic aldoximes, which exist only as anti isomers, and ketoximes can be separated almost completely and obtained as a syn isomer and an anti isomer.

III.A.2. Biological importance of oxime derivatives

Oxime functionality is also an important structural feature in several biologically active compounds. For example, perillartine (**1**), an oxime of perillaldehyde, is about 2000 times as sweet as sucrose and pralidoxime (**2**) and obidoxime (**3**) (**fig.III.A.2.**) are important antidotes for organophosphate poisoning. Recently, oxime ether derivatives have drawn much attention in medicinal research due to their significant bioactivity. Interestingly some oxime ether compounds exhibited not only excellent insecticidal activities but have also good plant growth regulatory activities.

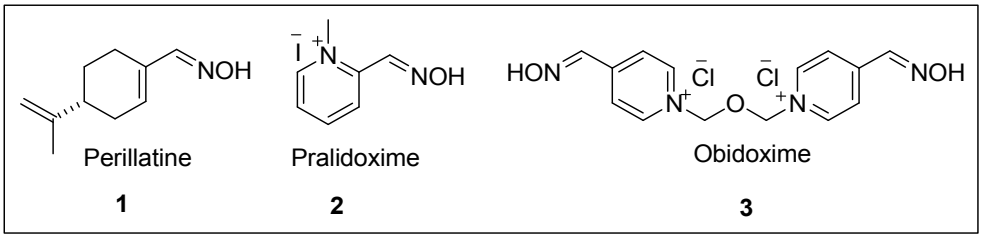


Fig.III.A.2. Biologically active oxime derivatives

The other biologically important oxime derivatives of various organic compounds are 5, 5'-substituted indirubin-3'-oxime derivatives found potent cyclin-dependent kinase inhibitors with anticancer activity (**fig.III.A.3.**).[1] Yeon Tae Jeong et al.[2] have reported in vitro antimicrobial activity against a panel of pathogenic bacteria and fungi from the oxime derivatives of substituted 2, 4, 6, 8-tetraaryl-3, 7-diazabicyco[3.3.1]nonan-9-ones. The moderate antimicrobial properties of some homo- and heteronuclear Cu(II) and Ni(II) complexes of new oxime-type ligands against several pathogenic microorganisms is reported by Ahmet Colak et al.[3] Alex W. White et al.[4] have reported the biological evaluation of a novel series of pyrroloazepinone and indoloazepinone oximes which showed promising growth inhibition activity against four human cancer cell lines. Shaoshun Li et al.[5] have reported the cyctotoxic activity of alkannin and shikonin oxime derivatives against three kinds of tumor cells and a normal cell line and

found some oxime derivatives were more or comparatively effective to the lead compounds, especially their selective and excellent antitumor activities towards K562 cells with no toxicity in normal cells.

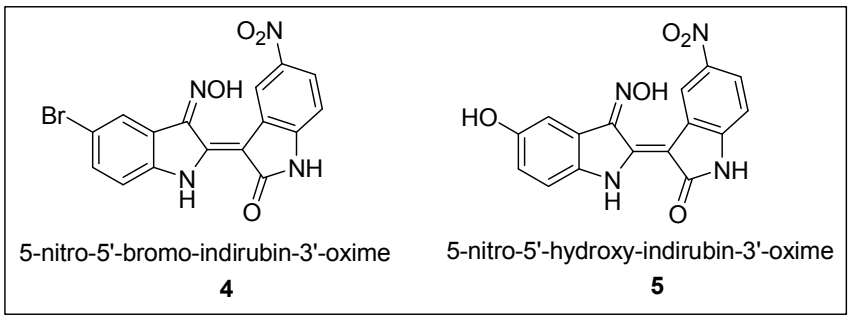


Fig.III.A.3. Biologically potent oxime derivatives

III.A.3. Application of oximes in organic transformations

III.A.3.1. Synthesis of amides, lactams and nitriles from oxime

Oximes are used extensively for the protection of carbonyl function. This compounds not only represents the series of derivatives of carbonyl compounds but also used as useful intermediate for the important organic synthesis and functional group transformations. Particularly, the manufacture of cyclohexanone oxime represents a key step in the sequence of the nylon 6 production. Inspite of having a huge industrial and medicinal uses, the other important and interesting application of oximes is functional group transformations and synthesis of nitrogen containing heterocycles such as Beckmann rearrangement for the synthesis of amide from ketoxime which requires high temperature and strongly acidic dehydrating media. Recently reported advance methodologies for the preparation of amide from ketoximes includes, organocatalyst cyanuric chloride catalyzed Beckmann rearrangement of ketoximes into amides under mild condition with HCl and $ZnCl_2$ as effective cocatalyst and successfully achived Beckmann rearrangement of six- to eight-membered cycloalkanone oximes,[6] perfluoroalkylsulfonyl fluoride-mediated abnormal Beckmann rearrangement for the transformation of steroid 17-oximes to the corresponding alkene nitriles regioselectively,[7] pivaloyl chloride/DMF a mild inexpensive and non-toxic system for the conversion of oximes to corresponding amides,[8] triphosphazene (**TAPC fig.III.A.4.**) catalyzed Beckmann rearrangement of ketoximes to lactams,[9] mercury-

catalyzed rearrangement of ketoximes into amides and lactams,[10] ruthenium-catalyzed oxime to amide rearrangement.[11]

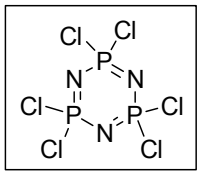
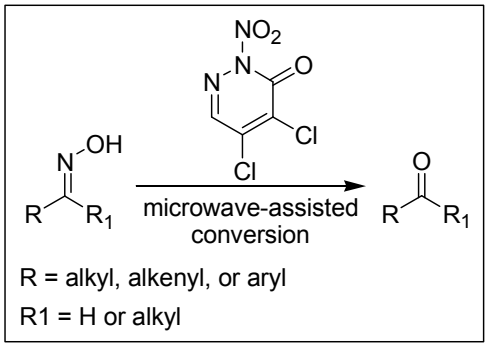


Fig.III.A.4. Triphosphazene (TAPC)

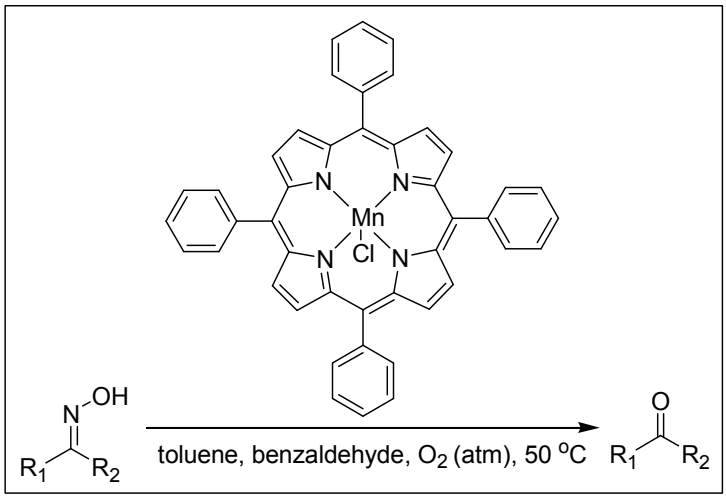
III.A.3.2. Regeneration of carbonyl function from oxime

Oximes are very useful for protecting carbonyl groups in organic synthesis.[12] Oximes can be prepared from carbonyl and non carbonyl compounds.[13] Furthermore, their synthesis from non-carbonyl compounds provides an alternative way for preparation of aldehydes and ketones.[14] Numerous methodologies have been develop for the regeneration of carbonyl compounds from oxime derivatives and synthesis of carbonyl compounds from non carbonyl compound via oxime formations. Bhushan M. Khadilkar et al reported the oxidative cleavage of oximes to corresponding carbonyl by silica supported chromium trioxide,[15] photosensitized oxidative deprotection of oximes to their corresponding carbonyl compounds by platinum(II) terpyridyl acetylide complex,[16] transformation of oxime to carbonyl compounds with 2-Nitro-4, 5-dichloropyridazin-3(2*H*)-one[17] (**scheme.III.A.1.**),



Scheme.III.A.1. Transformation of oximes to carbonyl compounds in the presence of 2-Nitro-4, 5-dichloropyridazin-3(2*H*)-one

the regeneration of carbonyl functionalities of aromatic compounds in the presence of tetrapyridine silver(II) peroxydisulfate in both acetonitrile and aqueous media,[18] oxidative cleavage of oximes with NBS in the presence of β-cyclodextrin in water,[19] oxidative deprotection of oximes to carbonyl compounds by 2, 6-Dicarboxypyridinium chlorochromate,[20] an aaerobic oxidation of oximes to corresponding carbonyl compounds catalyzed by manganese porphyrin in the presence of benzaldehyde[21] (**scheme.III.A.2.**).

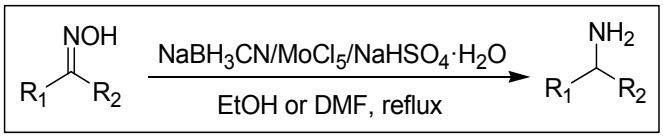


Scheme.III.A.2. Metalloporphyrins catalyzed oxidation of oximes to carbonyl compounds

III.A.3.3. Synthesis of amines from oxime

The conversion of carbonyl derivatives to amines via oxime is a useful transformation in the synthesis of numerous organic compounds and key intermediates in the biosynthesis of many pharmacological important compounds. Many synthetic routes have been reported for the facile synthesis of amines from oximes using various reductive systems such as, reduction of oximes to amines by catalytic transfer hydrogenation in the presence of magnesium powder and ammonium formate at room temperature,[22] reduction with $NaBH_4$ in MeOH in the presence of MoO_3 or $NiCl_2$,[23] conversion of aldoximes and ketoximes into amines in the presence of zinc dust and ammonium formate,[24] reduction of oximes to amines with zinc borohydride in the form of (pyridine)(tetrahydroborato)zinc complex,[25] reduction of oximes to primary and secondary amines in the presence of sodium borohydride-copper

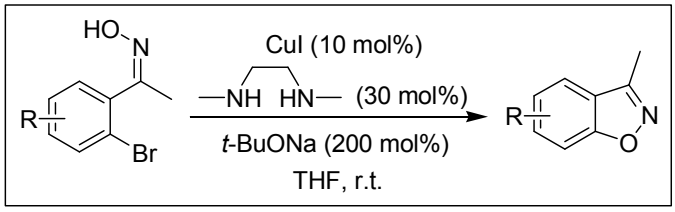
(II) sulphate in methanol,[26] $NaBH_3CN/MoCl_5/NaHSO_4 \cdot H_2O$ system for the reduction of various aldoximes and ketoximes to the corresponding amines[27] (**scheme.III.A.3.**).



Scheme.III.A.3. Synthesis of amines from oximes under reductive condition

III.A.3.4. Synthesis of heterocyclic compound from oxime

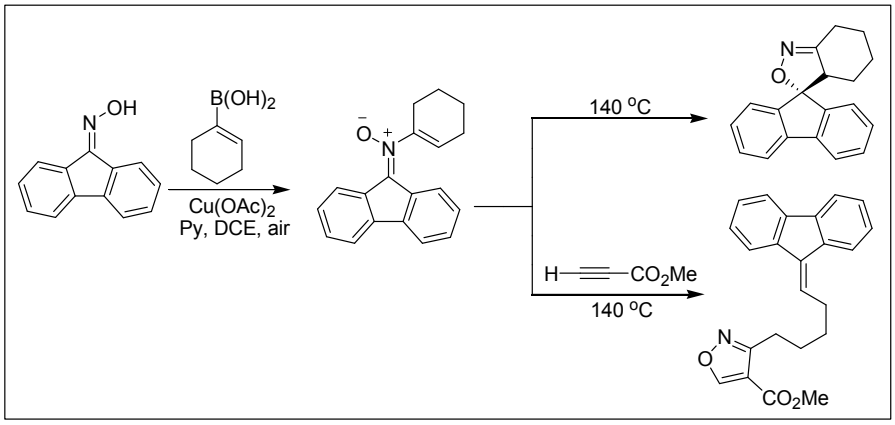
Not only functional group transformations but also oximes are equally useful for the synthesis of wide range of nitrogen containing heterocyclic compounds which contributes substructure of many bioactive natural products and structural motif of pharmaceutically important class of compounds. Literature review reveals the synthesis of large varieties heterocyclic compounds by taking oximes as starting material under different catalytic or reaction conditions such as the synthesis of variety of isoxazolines or isoxazoles from oximes and alkenes/alkynes in the presence of tert-butyl hypoiodite,[28] synthesis of annulated oxazoles by unprecedented cyclizations of α-oxo-oximes on heating with dimethyl sulfate, alkyl or aralkyl halides in DMF and in the presence of anhydrous potassium carbonate,[29] copper-catalyzed preparation of 3-methyl-1, 2-benzisoxazoles[30] (**scheme.III.A.4**), synthesis of isoquinolines by cationic ruthenium catalysts for alkyne annulations with oximes by C−H/N−O functionalizations,[31] synthesis of polysubstituted, aluminoisoxazoles and pyrazoles by a metalative cyclization.[32]



Scheme.III.A.4. Copper-catalyzed cyclization of *Z*-oximes into 3-methyl-1,2-benzisoxazoles

Laura L. Anderson et al.[33] reported the synthesis of spiroisoxazolines and fluorene-tethered isoxazoles by copper-mediated coupling between fluorenone oxime and vinyl

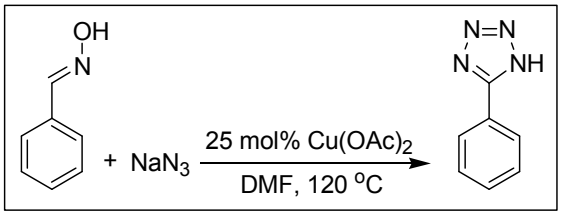
boronic acids via nitrone intermediate formation (**scheme.III.A.5**). Frank Glorius et al.[34] reported Rh(III) catalyzed synthesis of multisubstituted isoquinoline and pyridine N-oxides from oximes and diazo compounds exploring the application of oximes in heterocyclic synthesis.



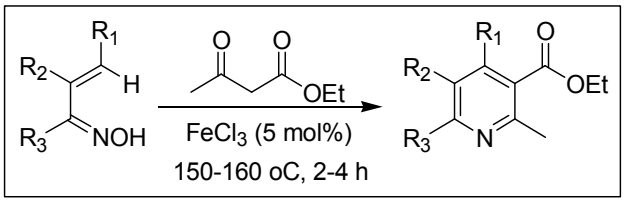
Scheme.III.A.5. Synthesis of spiroisoxazolines and fluorene-tethered isoxazoles by copper-mediated coupling between fluorenone oxime and vinyl boronic acids

There are numerous reports in the literature where oximes act as a starting material for the heterocyclic synthesis such as synthesis of quinoxalines by cyclization of α-arylimino oximes of α-dicarbonyl compounds,[35] rhodium catalyzed synthesis of isoquinolines and tetrahydroquinolines from ketoximes and alkynes by C-H bond activation,[36] solvent free synthesis of 2, 4, 6-triarylpyridines from acetophenone oximes and epoxy styrenes under neutral condition,[37] synthesis of isoindole from ortho-substituted aryl oximes sp^3 C-H activated cyclization,[38] synthesis of 5-substituted 1*H*-tetrazoles from various oximes and sodium azide (NaN_3) by using copper acetate as a catalyst[39] (**scheme.III.A.6.**), base promoted cyclocondensation of *C*-chloro oximes with cyclic 1, 3-diketones affords functionalized isoxazoles,[40] synthesis of 2, 4, 5-triaryl imidazoles from ketoximes via cyclization to the *N*-hydroxyimidazole and an unprecedented in situ thermal reduction of the N-O bond upon microwave irradiation at 200 °C,[41] the synthesis of 1*H*-indazoles from o-aminobenzoximes by the selective activation of the oxime in the presence of the amino group. A variety of substituted o-aminobenzoximes using a slight excess of methanesulfonyl chloride and triethylamine

at 0-23 °C were presented.[42] $FeCl_3$-catalyzed reaction of α, β-unsaturated oximes with ethyl acetoacetate to produce substituted nicotinic acid derivatives[43] (**scheme.III.A.7.**).



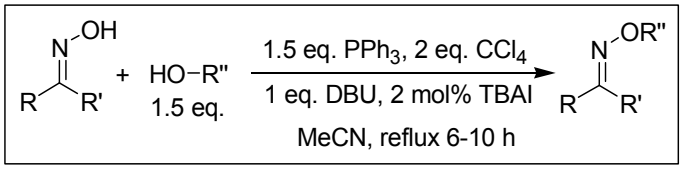
Scheme.III.A.6. Copper acetate catalyzed synthesis of 5-substituted 1*H*-tetrazoles from various oximes and sodium azide



Scheme.III.A.7. Synthesis of nicotinic acid derivatives from oximes

III.A.3.5. Synthesis of oxime ethers from oxime

Recently, oxime ether derivatives have drawn much attention in medicinal research due to their significant bioactivity.[44] Interestingly, Sun and co-workers found that some oxime ether compounds exhibited not only excellent insecticidal activities but have also good plant growth regulatory activities.[45] Such class of medicinally important compounds can be directly synthesize from oximes. Oximes are attractive synthetic reagents since they have both nitrogen and oxygen atoms as nucleophiles. Literature review reveals that numerous synthetic protocols have been developed to design and construct the oxime ethers of various compounds using oxime as a starting material such as Triphenylphosphine catalyzed synthesis of oxime ether by Michael addition of oximes onto activated olefins,[46] synthesis of oxime ethers by the treatment of alcohols with a mixture of triphenylphosphine, carbon tetrachloride, oxime, and DBU in the presence of catalytic amounts of tetrabutylammonium iodide in refluxing acetonitrile[47] (**scheme.III.A.8.**), synthesis of 3-trifluoromethyl substituted pyrazole oxime ether derivatives containing a pyridyl moiety,[48] palladium catalyzed synthesis of allylated oxime ethers.[4]



Scheme.III.A.8. Synthesis of oxime ethers by the combination of oximes and alcohol

III.A.4. Synthesis of oxime derived ligands and its importance in organic synthesis

Oximes play an important role in the development of transition metal coordination chemistry due to their versatile bonding modes. Oximes and their metal complexes are of current interest for their various physicochemical properties, reactivity patterns and potential applications in many important chemical processes in medicine and catalysis. The aryl palladium complexes especially ortho functionalized aryl complexes have the numerous interesting applications in organic synthesis. Catalytic C−C or C−heteroatom coupling reactions are usually carried out in the presence of aryl palladium complexes with nucleophiles. Oxime based palladacycles have gained a special attention in modern organic synthesis due their ubiquitous use in variety of catalytic transformations, such as oxime palladacycle derived from 4, 4'-dichlorobenzophenone catalyzed Sonogashira reaction of aryl iodides and aryl bromides with terminal acetylenes[50] using 1 equivalent of tetrabutylammonium acetate in organic solvents generally in 1 h at 110 °C, 4-hydroxyacetophenone oxime-derived palladacycle catalyzed cross-coupling reaction of potassium aryltrifluoroborates with aryl and heteroaryl chlorides in refluxing aqueous media,[51] *p*-hydroxyacetophenone oxime-derived palladacycle catalyzed Heck coupling reaction in refluxing water,[52] fluorous oxime palladacycle catalyzed cross-coupling reaction (Suzuki-Miyaura, Sonogashira, Stille, Heck and Kumada) both in organic and aqueous media,[53] oxime-derived palladacycles with pyridine co-ligand catalyzed intra-molecular Pauson–Khand reaction.[54]

III.A.5. Classical method for preparation of oxime

Classically, oximes are prepared by refluxing an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride and pyridine. The method has multiple drawbacks such as low yields, long reaction time, toxicity of pyridine, and effluent pollution caused by the use of organic solvent. The condensation of aldehydes with

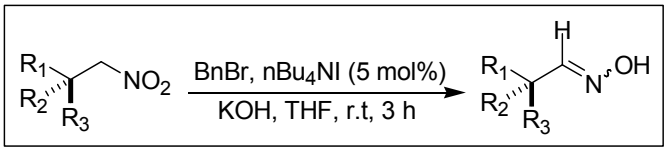
hydroxylamine gives aldoxime, and ketoxime is produced from ketones and hydroxylamine.

III.A.6. Modern methods for the synthesis of oxime from different functional groups

III.A.6.1. Synthesis of oxime from nitroalkanes

One of the preparatory methods of oximes is controlled reduction of nitro group. In the presence of strong reducing agents, nitro groups get converted into primary amines.

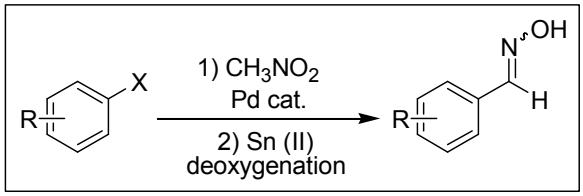
Erick M. Carreira et al.[55] have reported the synthesis of chiral adloxime from optically active nitro alkanes (**scheme.III.A.9.**) in the presence of benzyl bromide (BnBr), KOH, and *n*Bu_4NI in THF at room temperature.



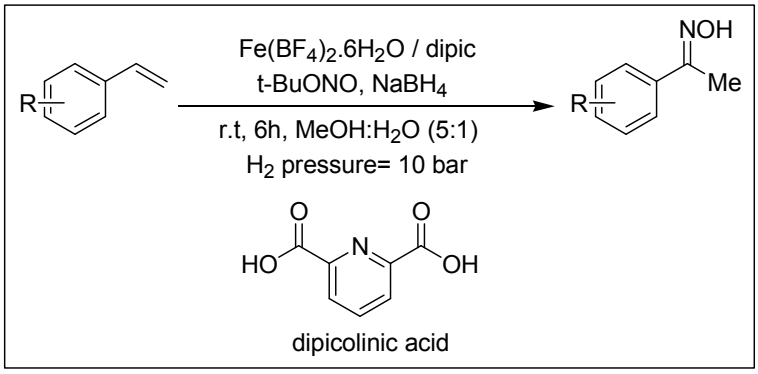
Scheme.III.A.9. Transformations of chiral nitroalkanes into chiral oximes

III.A.6.2. Miscellaneous methods for the preparation of oxime

The other methods include palladium catalyzed cross-coupling reaction of aryl halides and nitromethane under Nef conditions[56] (**scheme.III.A.10.**), $Fe(BF_4)_2.6H_2O$/ 2, 6-pyridinedicarboxylic acid catalyzed a selective synthesis of oximes in the presence of t-BuONO/$NaBH_4$ under H_2 pressure (10 bar) in MeOH–H_2O (5 : 1) from styrene derivatives [57] (**scheme.III.A.11.**), gold catalysts chemoselective route to synthesize oximes by hydrogenation of α, β-unsaturated nitrocompounds with H_2.[58]

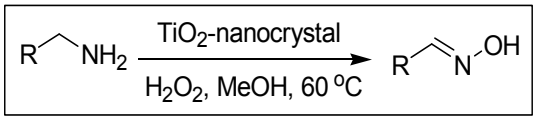


Scheme.III.A.10. Palladium catalyzed synthesis of oximes by cross-coupling between aryl halide and nitro alkane under reductive condition

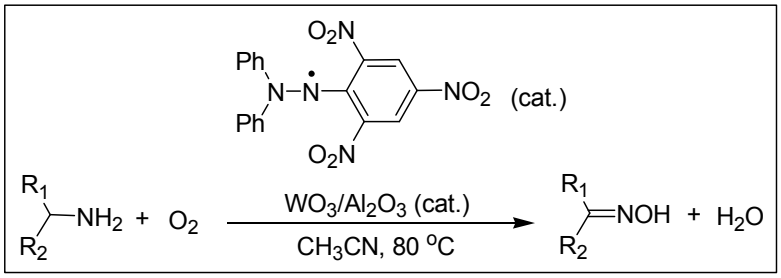


Scheme.III.A.11. Iron catalyzed synthesis of oximes from alkenes

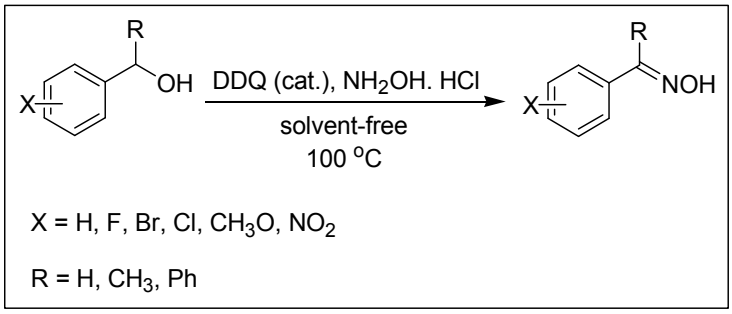
Oxime can also be directly synthesized from primary amine by mild oxidation. Jack K. Crandall et al.[59] reported the oxidation of primary amines where several primary amines have been oxidised with dimethyldioxirane under variety of conditions, selective catalytic oxidation of benzylic and allylic amines to oximes with H_2O_2 over TS-l (titanium silicalite) is reported by A. Sudalai et al.[60] The similar type of synthesis preparation of oximes by oxidation of Primary aliphatic amines with α- hydrogen atoms in the presence of hydrogen peroxide as oxidant and catalytic quantities of titanium silicalite molecular sieves to corresponding oximes is reported by J. Sudhakar Reddy et al.[61] The recent literature report for the conversion of amines to oximes include oxidation of aliphatic and aromatic amines into corresponding oximes using heterogenous nanocrystalline titanium (IV) oxide as catalyst and H_2O_2 as oxidising agent[62] (**scheme.III.A.12.**), oxidation of primary amines to oximes with molecular oxygen using 1, 1-Diphenyl-2-picrylhydrazyl and WO_3/Al_2O_3 as catalysts[63] (**scheme.III.A.13.**), synthesis of aldoximes and ketoximes from primary and secondary benzyl alcohol in the presence of hydroxylamine hydrochloride and catalytic amount of 2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ) under solvent free condition[64] (**scheme.III.A.14.**), synthesis of oximes by benzylic C-H functionalization of azaarenes by its nuleophilic addition to nitroso compound[65] (**scheme.III.A.15.**), one-pot conversion of methyl arenes into aryl oxime with N-bromo succinamide (NBS), benzoyl peroxide, hydroxylamine hydrochloride and a base triethylamine in pyridine/DMF at reflux conditions.[66]



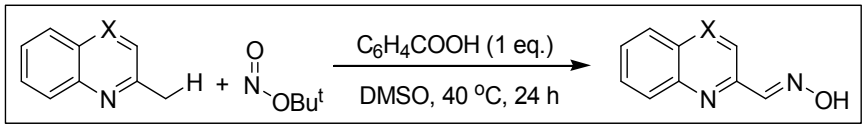
Scheme.III.A.12. Nanocrystalline titanium (IV) oxide catalyzed synthesis of oximes from amines



Scheme.III.A.13. Transformation of primary amines to oximes



Scheme.III.A.14. Synthesis of oximes from benzylic alcohols

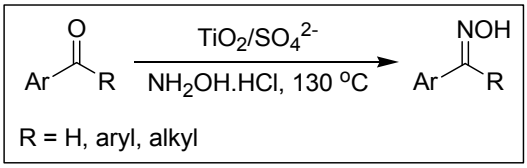


Scheme.III.A.15. Synthesis of oximes by benzylic C-H functionalization

III.A.6.3. Synthesis of oxime from carbonyl compounds

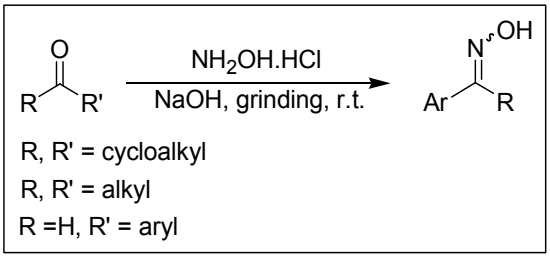
The draw backs of classical method for the preparation of oxime which include pyridine in alcoholic solution of carbonyl compounds and hydroxylamine hydrochloride at elevated temperature; there was a need for the improvement of the complex classical method to simple one. Many improvements regarding the classical method have been done in the past years such as preparation of oximes on silica in the presence of sodium hydroxide,[67] microwave assisted solvent free synthesis of oximes from aldehydes or

ketones on hydroxylamine hydrochloride impregnated wet basic alumina,[68] synthesis of aromatic oximes by reaction of aromatic aldehydes and ketones with hydroxylamine hydrochloride catalyzed by TiO_2/SO_4^{2-} solid superacid[69] (**scheme.III.A.16.**), preparation of cyclohexanone oxime from cyclohexanone and aqueous hydroxylamine in recyclable reaction media ionic liquid (bmiBF4) at room temperature without any other additives.[70]



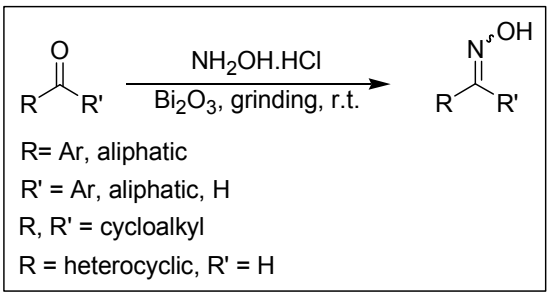
Scheme.III.A.16. TiO_2/SO_4^{2-} catalyzed synthesis of aromatic oximes from carbonyl compounds

The conversion of alicyclic, aliphatic and aromatic aldehydes into the corresponding oximes by simple grinding the aldehydes, hydroxylamine hydrochloride and sodium hydroxide without solvent at room temperature was also successfully made. However, this procedure was unsuccessful in the case of aromatic ketones. In this case it was necessary to add silica gel as a catalyst[71] (**scheme.III.A.17.**).

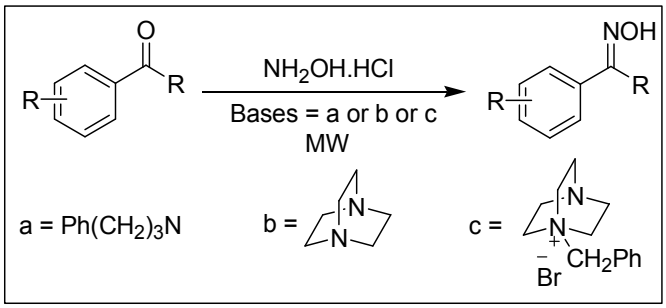


Scheme.III.A.17. Synthesis of oximes from carbonyl compounds in the presence of sodium hydroxide as base

Ashim Jyoti Thakur et al.[72] recently reported the solvent-free conversion of carbonyl compounds into corresponding oximes by simply grinding the reactants in the presence of Bi_2O_3 (**scheme.III.A.18.**). A. R. Hajipour et al.[73] reported the chemoselective method for the preparation of aldoximes using microwave irradiation in the presence of tribenzylamine or 1, 4-diazabicyclo[2.2.2]octane or 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane bromide as bases (**scheme.III.A.19.**).



Scheme.III.A.18. Conversion of carbonyls into oximes in presence of Bi_2O_3



Scheme.III.A.19. Synthesis of oximes from carbonyls under microwave irradiation

III.A.7. Conclusion

As oxime derivatives have enormous applications in the area of pharmaceutical as well as organic transformation. The substantial amount of methodologies for the oxime preparation from different functionality and under different catalytic conditios is reported in the literature. Most of the reported methodologies are not straight-forward, green and selective. Therefore, based on the above literature, it appeared that there is still a demand of green, selective, and easy reaction protocol for the synthesis of oxime derivatives.

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III.A.8. References

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CHAPTER III

SECTION-B

Solid phase synthesis of oxime derivatives

III.B. Present Investigation

III.B.1. Background of the present investigation

Oximes are highly valuable organic molecules considering their numerous applications for polymers,[1] fungicides,[2] biochemicals,[3] fragrances.[4] Oximation is very efficient method for characterization and purification of carbonyl compounds. The manufacture of cyclohexanone oxime represents a key step in the sequence of the Nylon 6 production. Synthesis of oximes is considered as a important reaction in organic chemistry because these compounds not only represents a series of useful derivatives of carbonyl compounds but also considered as a versatile organic intermediated for the synthesis of wide range of heterocyclic compounds such as quinoxaline,[5] imidazole,[6] oxadiazole,[7] oxazole,[8] oxazoline.[9] Beside these, oximes are used for the ample of functional group transformation which comprises conversions into nitriles,[10] nitro compounds,[11] nitrones,[12] amines.[13] Oximes act as a versatile ligand for several metal catalyzed organic synthesis.[14]

Oximes play an important role as ligands for transition metals. Oxime based palladacycles have gained a special attention in modern organic synthesis due to their ubiquitous use in variety of catalytic transformations. Catalytic C−C or C−heteroatom coupling reactions are usually carried out in the presence of aryl palladium complexes with nucleophiles such as oxime palladacycle derived from 4, 4'-dichlorobenzophenone catalyzed Sonogashira reaction,[15] oxime-derived palladacycle catalyzed cross-coupling reaction of potassium aryltrifluoroborates with aryl and heteroaryl chlorides,[16] *p*-hydroxyacetophenone oxime-derived palladacycle catalyzed Heck coupling reaction,[17] fluorous oxime palladacycle catalyzed cross-coupling reaction (Suzuki-Miyaura, Sonogashira, Stille, Heck and Kumada),[18] oxime-derived palladacycles with pyridine co-ligand catalyzed intra-molecular Pauson–Khand reaction.[19]

Classically, oximes were prepared by refluxing an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride and pyridine. The method has multiple

drawbacks such as low yields, long reaction time, toxicity of pyridine, and effluent pollution caused by the use of organic solvent.

In recent years, solvent free reactions have drawn considerable interest and popularity[20] not only from the environmental aspect but also for the synthetic advantages in terms of yield, selectivity and simplicity of the reaction procedure. Several procedures for the preparation of oximes exist, but, most of them have not addressed the green chemistry issue. They are associated with generation of pollutants, requirement of high reaction temperature, low yields, and waste of metal salts in the environment. Over the last decades, several protocols have been developed for the synthesis of oximes from carbonyl compounds. A. R.Hajipour et al.[21] reported the solid phase synthesis of oximes from carbonyl compounds and hydroxylamine hydrochloride in the presence of sodium hydroxide. The use of strong base has reduced its application as a green and selective protocol. The a number of reagent and catalyst have been used for the transformation of carbonyl compounds into oximes such as preparation of oximes from aldehydes or ketones and hydroxylamine hydrochloride impregnated wet alumina under microwave irradiation,[22]

TiO_2/SO_4^{2-} solid superacid catalyzed synthesis of aromatic aldoximes and ketoximes under solvent free condition,[23] prepraration of cyclic ketoximes using aqueous hydroxylamine in ionic liquids ($bmiBF_4$),[24] solvent free synthesis of alicyclic, aliphatic carbonyl compounds and aromatic aldehydes into the corresponding oximes by grinding the carbonyl compounds, hydroxylamine hydrochloride and sodium hydroxide,[25] synthesis of oximes from carbonyl compounds in the presence of Bi_2O_3 by simple grinding the reactants,[26] synthesis of aldoximes under microwave irradiation using *in situ* generated ionic liquids.[27]

Synthesis of oximes provides not only reaction intermediates but also the preparation of carbonyl compounds from non carbonyl compounds. There is substantial report in literature of the synthesis of oximes from non carbonyl compounds such as reduction of nitro alkane to oximes in the presence of benzyl bromide, KOH, and $n Bu_4NI$ in THF at room temperature,[28] palladium catalyzed cross-coupling reaction of aryl halides and nitromethane under Nef conditions,[29] oxidation of aliphatic and aromatic amines into corresponding oximes using heterogenous nanocrystalline titanium (IV) oxide as catalyst and H_2O_2 as oxidising agent,[30] synthesis from primary and secondary benzyl

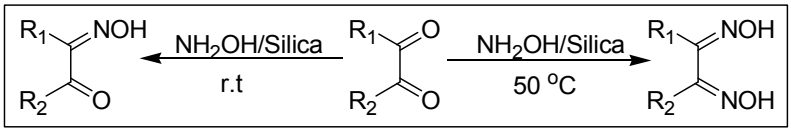
alcohol in the presence of hydroxylamine hydrochloride and catalytic amount of 2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ) under solvent free condition.[31]

Such a huge application of oximes and also the associated drawback of traditional method of its preparation such as no selectivity, use of hazardous chemicals, high cost, poor chemical yields, requirements of long reaction time and tedious work-up procedures, has limit their use under the aspect of chemical selectivity as well as environmentally benign process. Reports are still scanty towards the development of a simple, selective and greener protocol for the preparation of such an important class of derivatives.

Sustainable development can be defined as the ability to meet the needs of the current generation while preserving the ability of future generations to meet their needs. Green chemistry is one way to achieve it. Several ways are known through which a reaction can be said to be clean and green. There is a need for a process that involves multiple chemical transformations in a single-pot with minimal work up and less waste generation.

In recent years, silica gel have attracted intensive interest for their being a possible replacement of traditional solvents for organic synthesis, particularly in the area of green chemistry, due to their advantageous properties, including non toxic medium for organic reactions, high thermal and chemical stability. Hence, there is a demand for developing an efficient, convenient, and non-polluting or less polluting alternative method for the preparation of oximes. So, the development of easy and clean procedures for obtaining this oxime results in high interest.

It was therefore felt necessary to develop selective, easy, safe and green procedure for oxime synthesis. In view of the above and in continuation our studies towards the development of greener methodology for organic transformation,[32] In this chapter, we have reported a very simple, highly selective and green protocol for oxime preparation from carbonyl compounds. The beauty of the protocol has been its selectivity that can be applied either for exclusively monoxime or dioxime preparation from symmetrical 1, 2 dicarbonyl system or from 1, 2 unsymmetrical dicarbonyl systems by regioselective pathway (**scheme.III.B.1**).



Scheme.III.B.1. Selective synthesis of mono and dioxime from 1, 2 dicarbonyl compounds

III.B.2. Results and discussion

To cope up with the growing demand towards the development of greener protocols for organic transformation, our laboratory has devoted a significant effort to develop efficient protocols for the preparation of a diverse collection of organic derivatives from common intermediates following simple and greener methodologies. The present investigation has developed a clean and selective method for the synthesis of oxime derivatives from a wide variety of carbonyl compounds.

A model study with benzil on silica – $NH_2OH.HCl$ at room temperature (vide infra) gave an excellent yield of the monoxime and at elevated temperature gave excellent yield of dioxime. Since no selective protocol is being reported so far either for exclusive formation of monoxime or dioxime from a 1, 2 dicarbonyl compounds, a change in reaction temperature and in the molar proportion of the reactants (**table.III.B.1**) induces selectivity in the protocol towards monoxime and/or dioxime formation from 1, 2 dicarbonyl system. For example, benzil and hydroxyl amine hydrochloride in the mol ratio of 1:1.2 afforded only the monoxime (97%), at room temperature and 1:2.2 mol ratio of the same combination yielded exclusively the dioxime at 50 ^oC (**entries 1-2, table.III.B.1**). Similar result was also obtained with phenyl glyoxal (**entry 3-4, table.III.B.1**) as a dicarbonyl compounds. Among the two different carbonyl groups in phenyl glyoxal only aldehyde function takes part in the formation of monoxime following regioselective pathway.

Table.III.B.1

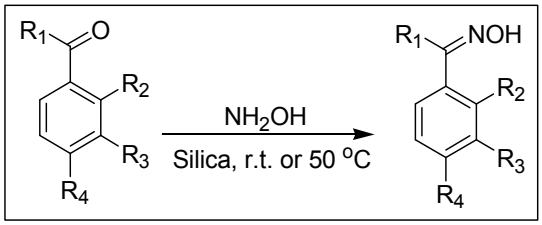
Selective synthesis of mono and dioxime from 1, 2 dicarbonyl system

						Yield (%)[b]	
Entry	R_1	R_2	Mol ratio[a]	Temp (^oC)	Time (h)	Monoxime	Dioxime
1	Ph	Ph	1:1.2	r.t	6	97	nil
2	Ph	Ph	1:2.2	50	5	nil	95
3	H	Ph	1:1.2	r.t	3	97	nil
4	H	Ph	1:2.2	50	4.3	nil	96

[a]Mol ratio of 1, 2 dicarbonyl and hydroxyl amine.

[b]Isolated yield.

Several experiments were then carried out with a wide variety of aromatic monocarbonyl compounds to explore the potential of the newly developed method as a general protocol for synthesis of oximes (**scheme.III.B.2.**) (**table.III.B.2**). In deciding the best reaction condition for the above transformation, aromatic aldehydes having electron withdrawing (**entries 1-4, table.III.B.2**) as well as electron donating group (**entries 5-9, table.III.B.2**) were tried in comparison to the unsubstituted substrate (**entry 10, table.III.B.2)** in the above protocol and the transformation was found independent on the nature of substituent (**scheme.III.B.2**). The study also indicated that aromatic carbonyl compounds with electron withdrawing substituents mostly at *ortho*- or *para*- position gave best results at room temperature and those having electron releasing substituents needed a higher temperature (50 ^oC) to yield the maximum product (**entries 7, 8, 9, 11, 12, table.III.B.2**).



Scheme.III.B.2. Synthesis of oxime from aromatic monocarbonyl compounds

Table.III.B.2.

Synthesis of oxime from aromatic monocarbonyl system

Entry	R_1	R_2	R_3	R_4	Time (h)	Temp (^oC)	Yield (%)[b]
1	H	NO_2	H	H	1.2	r.t	94
						50	96
2	H	H	NO_2	H	3	r.t	91
						50	97
3	H	H	H	NO_2	1.2	r.t	95
						50	98
4	H	H	H	F	4	r.t	94
						50	98
5	H	OH	H	H	5	r.t	90
						50	92
6	H	H	H	OH	5	r.t	91
						50	92
7	H	OH	OMe	H	6.3	r.t	18
						50	86
8	H	H	OMe	OH	6	r.t	24
						50	89
9	H	H	H	NMe_2	5	r.t	28
						50	84
10	H	H	H	H	5	r.t	92
						50	93
11	Me	H	H	H	4.3	r.t	nil
						50	97
						r.t	nil

12	Ph	H	H	H	2.3	50	96

In order to establish the general applicability, we applied this present procedure on alicyclic carbonyl compounds, cyclohexanone (**entry 1, table.III.B.3**). Although yields are comparatively less, large molecule like steroidal ketone also showed identical result (**entry 4 table.III.B.3**).

However, alicyclic 1, 2 and 1, 3 dicarbonyl (**entry 2 and 3, table.III.B.3**) does not show the selectivity rather they only form the dioxime at room temperature as well as at elevated temperature.

Table.III.B.3

Synthesis of alicyclic and steroidal oximes

Entry	Carbonyls	Temp (^{o}C)	Time (h)	Yield (%)[b]	
				Monoxime	Dioxime
1	Cyclohexanone	r.t	3	95	Nil
		50	4	97	
2	Cyclohexa-1,2 dione	r.t	3	Nil	72
		50	3	Nil	94
3	Dimedone	r.t	3	Nil	62
		50	4	Nil	91
4	16-DPA	r.t	8	18	Nil
		50	6	42	

III.B.3. Experimental

III.B.3.1. Chemicals

All the chemicals which were used for the present investigation are listed in the **table.III.B.4.** The details of the chemicals regarding their source and purity are summarised in **table.III.B.4.**

Table.III.B.4.

Chemicals used for the present investigation

Entry	Chemical	Source	Purity (%)
1	Benzil	SRL	98
2	Phenyl glyoxal	Sigma-Aldrich	97
3	2-Nitrobenzaldehyde	LOBA Chemie	>99
4	3-Nitrobenzaldehyde	LOBA Chemie	98
5	4-Nitrobenzaldehyde	LOBA Chemie	99
6	4-Fluorobenzaldehyde	Fisher Scientific	>98
7	2-Hydroxybenzaldehyde	S.D Fine	99
8	4-Hydroxybenzaldehyde	S.D Fine	98
9	2-Hydroxy-3-methoxybenzaldehyde	ACROS	99
10	3-Methoxy-4-hydroxybenzaldehyde	S.D Fine	99
11	N,N-dimethyl-4-aminobenzaldehyde	Sigma-Aldrich	99
12	Benzaldehyde	Sigma-Aldrich	>99.5
13	Acetophenone	SRL	99.5
14	Benzophenone	SRL	99
15	Cyclohexanone	Alfa Aesar	>99
16	Cyclohexane-1, 2-dione	Sigma-Aldrich	97
17	Cyclohexane-1, 3-dione	Alfa Aesar	98
18	16-Dehydropregnenolone	-	-
19	Hydroxylamine hydrochloride	Fisher Scientific	96
20	Sodium sulphate anhydrous	SRL	99.5
21	Petroleum ether	Thomas Baker	98
22	Ethyl acetate	Thomas Baker	99
23	Diethyl ether	SRL	99.5

24	Silica gel 60-120 mesh	SRL	-
25	Silica gel for TLC	SRL	-
26	Potassium bromide for IR	Merck	99
27	$CDCl_3$ for NMR	ACROS	99.8
28	DMSO-d_6 for NMR	SRL	99.8

Entry 18 was prepared in the laboratory by reported protocol; the protocol is given in chapter II experimental.

III.B.3.2. Reaction procedure and purification

2g/mol silica gel (60-120 mesh) was taken on motor, mixed finely with carbonyl compound, add 1.2 mol of hydroxylamine hydrochloride for monoxime and 2.2 mol for dioxime and then mixed thoroughly with pestle. The reaction mixture was then allowed to stir at room temperature or at 50 ^{o}C as the case may be on a magnetic stirrer using oil bath. The completion of reaction was monitored by TLC. The product was extracted with ether, washed with water (30ml x 3), dried over anhydrous Na_2SO_4 and purified by column chromatography using neutral active alumina.

III.B.3.3. Spectroscopic measurements

IR spectra were recorded on KBr disks and nujol in the range 4000-400 on Perkin Elmer FT IR spectrometer.^{1}H NMR were recorded on 300 MHz and ^{13}C NMR were recorded on 75 MHz Bruker Avance FT NMR spectrometer using TMS as internal standard.

III.B.4. Conclusion

In conclusion, we have developed a highly selective, green, mild and highly efficient protocol for the synthesis of oximes from 1, 2 dicarbonyl compounds and wide varieties of aldehydes and ketones.

III.B.5. Spectroscopic data

The compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and comparing the melting point with authentic samples (**table.III.B.4**).

III.B.5.1. Benzil monoxime

IR (cm^{-1}, KBr): 3238, 1674, 1593. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.24-7.64 (m, 8H), 7.96-7.99 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 126.4, 128.2, 128.4, 128.9, 129.1, 129.4, 130.3, 130.5, 130.9, 134.6, 157.1, 194.2 ppm.

III.B.5.2. Benzil dioxime

IR (cm^{-1}, KBr): 3180, 1649, 1498. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.36-7.38 (m, 6H), 7.48-7.49(m, 4H), 11.49 (s, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 125.9, 129.1, 129.7, 133.2, 151.1 ppm.

III.B.5.3. Phenylglyoxal monoxime

IR (cm^{-1}, KBr): 3419, 1701, 1651, 1598. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.49-7.54 (m, 1H), 7.61-7.67 (m, 1H), 7.14-7.98 (m, 2H), 8.03 (s, 1H), 12.70 (s, 1H) ppm. ^{1}H NMR (75 MHz, DMSO-d_6): δ, 128.8, 130.0, 133.6, 136.5, 148.2, 189.5 ppm.

III.B.5.4. Phenylglyoxal dioxime

IR (cm^{-1}, KBr): 3421, 1618, 1511. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 6.31 (s, 1H), 7.46-7.51 (m, 3H), 7.81-7.89 (m, 3H), 9.14 (s, 1H) ppm. ^{1}H NMR (75 MHz, DMSO-d_6): δ, 128.4, 129.2, 131.4, 134.5, 147.3, 151.6 ppm.

III.B.5.5. 2-Nitro benzaldoxime

IR (cm^{-1}, KBr): 3390, 1662 1522. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.52-7.55 (m, 1H), 7.63-7.64 (m, 1H), 7.91-7.92 (m, 1H,), 8.91 (s, 1H), 8.11-8.19 (m, 1H), 8.28 (s, 1H) ppm.

III.B.5.6. 4-Nitro benzaldoxime

IR (cm^{-1}, KBr): 3396, 1667. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.83-7.87 (m, 2H), 8.23-8.30 (m, 3H), 11.97 (s, 1H), ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 123.9, 127.3, 139.4, 146.7, 147.4 ppm.

III.B.5.7. 4-Fluoro benzaldoxime

IR (cm^{-1}, KBr): 3262, 1512, 1321. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.11-7.24 (m, 2H), 7.52-7.61 (m, 2H), 8.13 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 115.7, 116.1, 128.6, 128.7, 149.1, 162.3, 165 ppm.

III.B.5.8. 2-Hydroxy benzaldoxime

IR (cm^{-1}, KBr): 3336, 1656, 1523. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 6.90-6.98 (m, 2H), 7.16-7.31 (m, 2H), 7.92 (s, 1H), 8.22 (s, 1H), 10.01 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 116.4, 116.6, 119.8, 130.7, 131.3, 152.9, 157 ppm.

III.B.5.9. 2-Hydroxy-3-methoxybenzaldoxime

^{1}H NMR (300MHz, $CDCl_3$): δ, 3.92 (s, 3H), 6.81-6.94 (m, 3H), 8.96 (s, 1H), 8.24 (s, 1H), 9.98 (s, 1H) ppm. ^{13}C NMR (75MHz, $CDCl_3$): δ, 56.1, 113.2, 116.6, 119.5, 122.2, 146.8, 148, 152.5 ppm.

III.B.5.10. 4-Hydroxy-3-methoxy benzaldoxime

^{1}H NMR (300 MHz, DMSO-d_6): δ, 3.72 (s, 3H), 6.68 (d, 1H, J=8.1 Hz), 6.89 (m, 1H), 7.12 (d, 1H, J=2 Hz), 7.88 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 55.6, 108.2, 115.1, 120.3, 124.2, 147.6, 147.8, 148.1 ppm.

III.B.5.11. 4-*N, N*-Dimethylaminobenzaldoxime

IR (cm^{-1}, KBr): 3241, 3127, 2976, 1609, 1554. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 2.96 (s, 6H,), 6.71(d, 2H, J=8.8 Hz), 7.39 (d, 2H, *J*=8 Hz), 7.89 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 41, 112.1, 121.4, 127.8, 149, 151.4

III.B.5.12. Benzaldoxime

IR (cm^{-1}, KBr): 3355, 1656, 1436. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.21-7.32 (m, 3H), 7.41-7.47 (m, 1H,), 7.75-7.79(m, 1H), 8.11 (s, 1H), 8.31 (s, 1H), ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 127, 128.8, 130.1, 131.8, 150.4.

III.B.5.13. Acetophenone oxime

IR (cm^{-1}, KBr): 3248, 1447, 1371. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 2.31 (s, 3H), 7.20-7.48 (m, 3H), 7.51-7.82 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 12.3, 126.2, 128.5, 129.2, 136.5, 156.1 ppm.

III.B.5.14. Benzophenone oxime

IR (cm^{-1}, KBr): 3214, 1557, 1377. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.08-7.13 (m, 1H), 7.32-7.38 (m, 2H), 7.50-7.62(m, 3H), 7.77-7.80 (m, 2H), 7.94-7.97 (m, 2H), 10.26 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO- d_6): δ, 120.8, 124.1, 128.1, 128.8, 129.0, 132, 135.4, 139.6, 166 ppm.

III.B.5.15. Cyclohexanone oxime

IR (cm^{-1}, KBr): 3291, 1665. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.48-1.69 (m, 6H), 2.11 (d, 2H, *J*=8Hz), 2.29 (t, 2H, J=8 Hz), 6.51 (s, 1H), ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 23.8, 24.3, 24.9, 27.5, 33.2, 158.2 ppm.

III.B.5.16

Some of the known oximes were characterized by comparing their melting point with authentic samples **table.III.B.5.**

Table.III.B.5.

Melting point comparison of known prepared oximes with authentic samples

Entry	Mp of prepared oxime (^{o}C)	Mp of authentic sample (^{o}C)
1	4-hydroxy benzaldoxime (83-86)	85
2	3-nitro benzaldoxime	123
3	Cyclohexane 1,2-dione-dioxime (190-193)	192
4	Dimedone-dioxime (172-175)	173
5	16-DPA oxime (222-225)	223-227

III.B.6. Supporting spectra

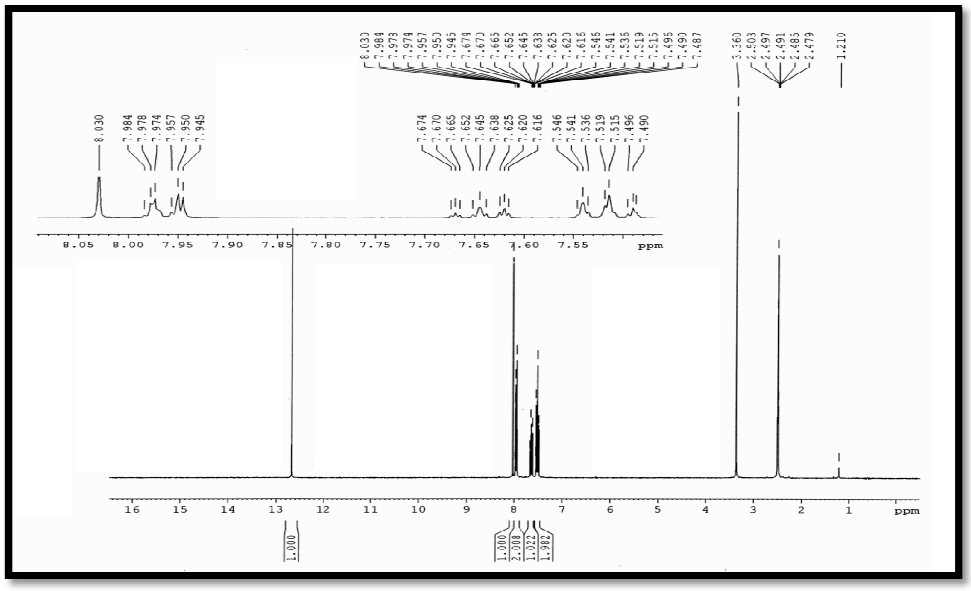


Fig.III.B.1. ^{1}H NMR spectrum of phenylglyoxal monoxime

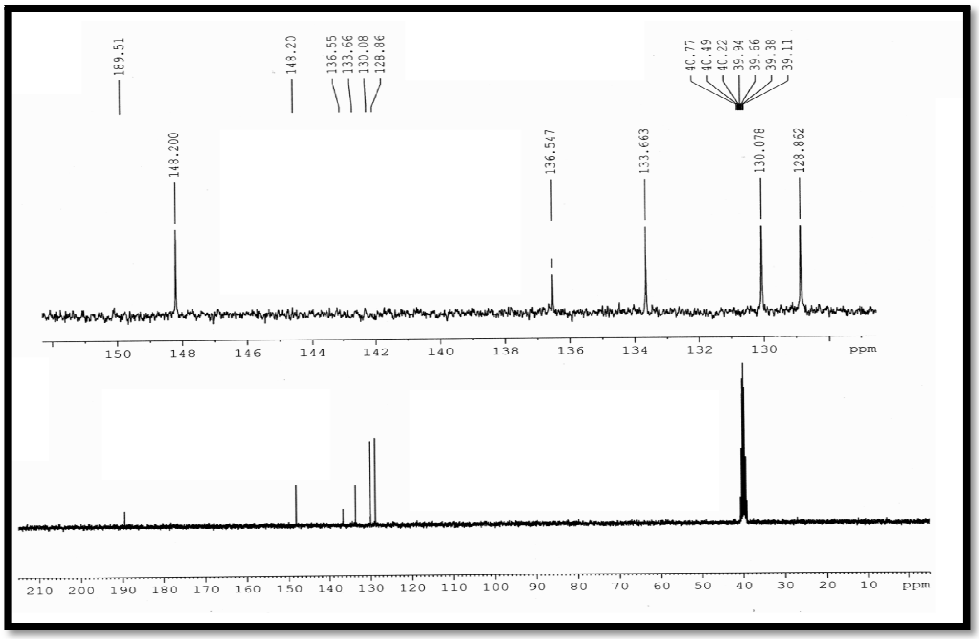


Fig.III.B.2. ^{13}C NMR spectrum of phenylglyoxal monoxime

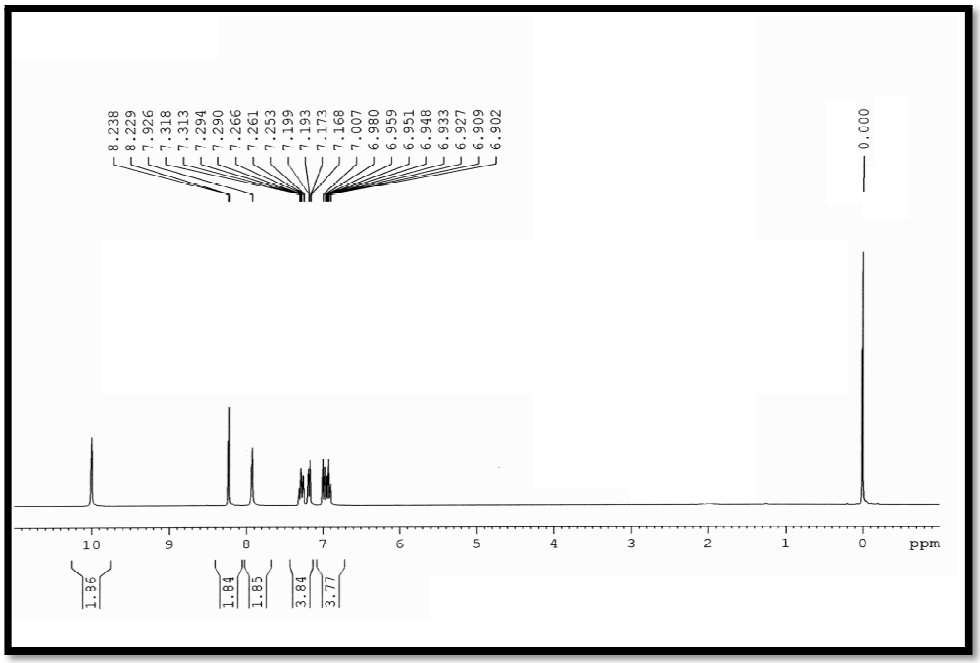


Fig.III.B.3. ^{1}H NMR spectrum of 2-Hydroxy benzaldoxime

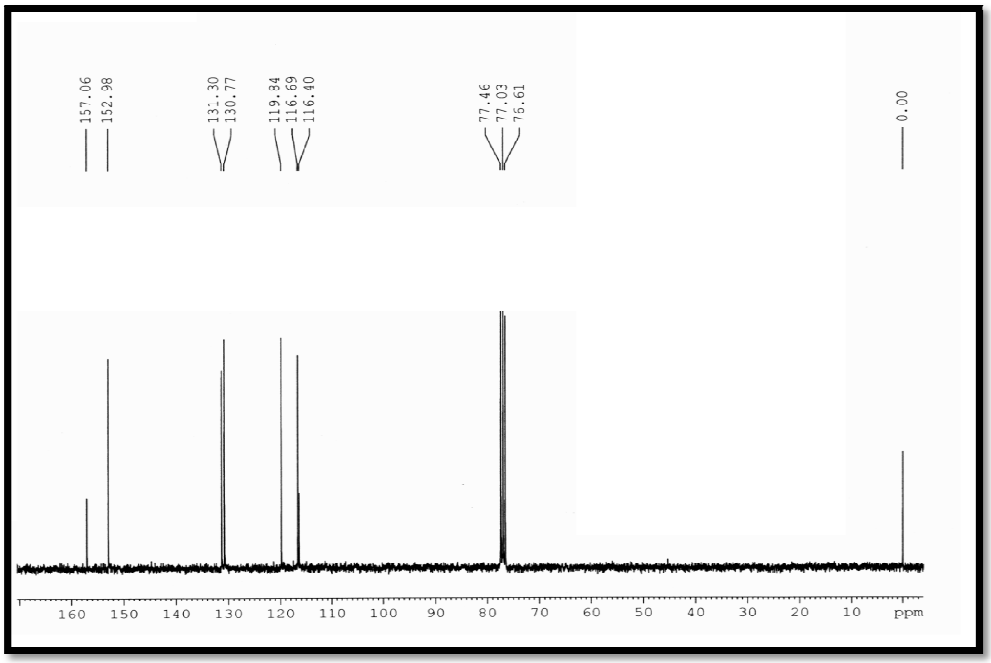


Fig.III.B.4. ^{13}C NMR spectrum of 2-Hydroxy benzaldoxime

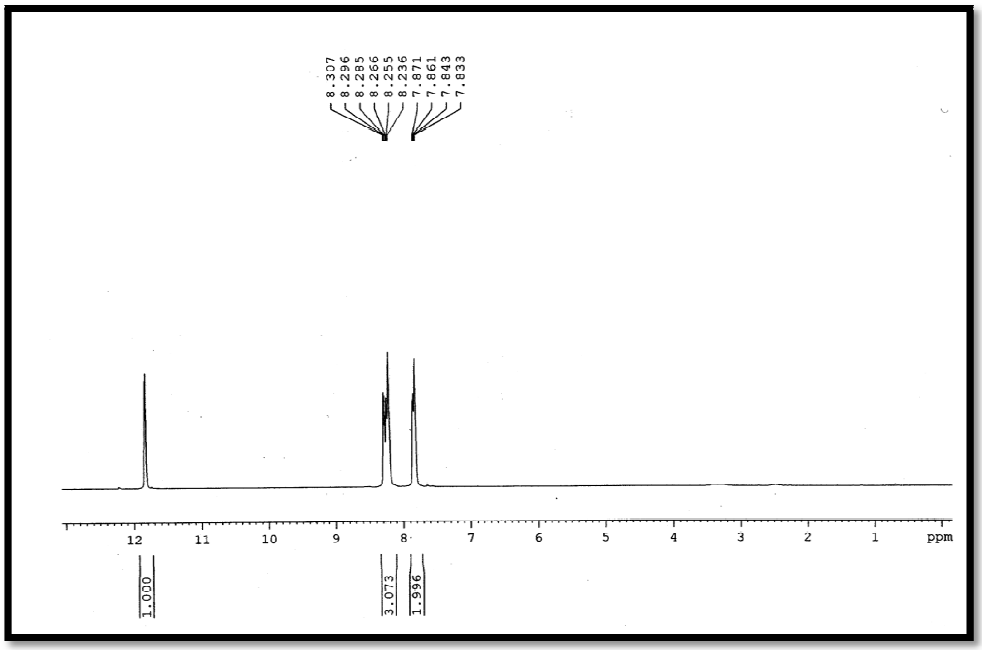


Fig.III.B.5. ^{1}H NMR spectrum of 4-Nitro benzaldoxime

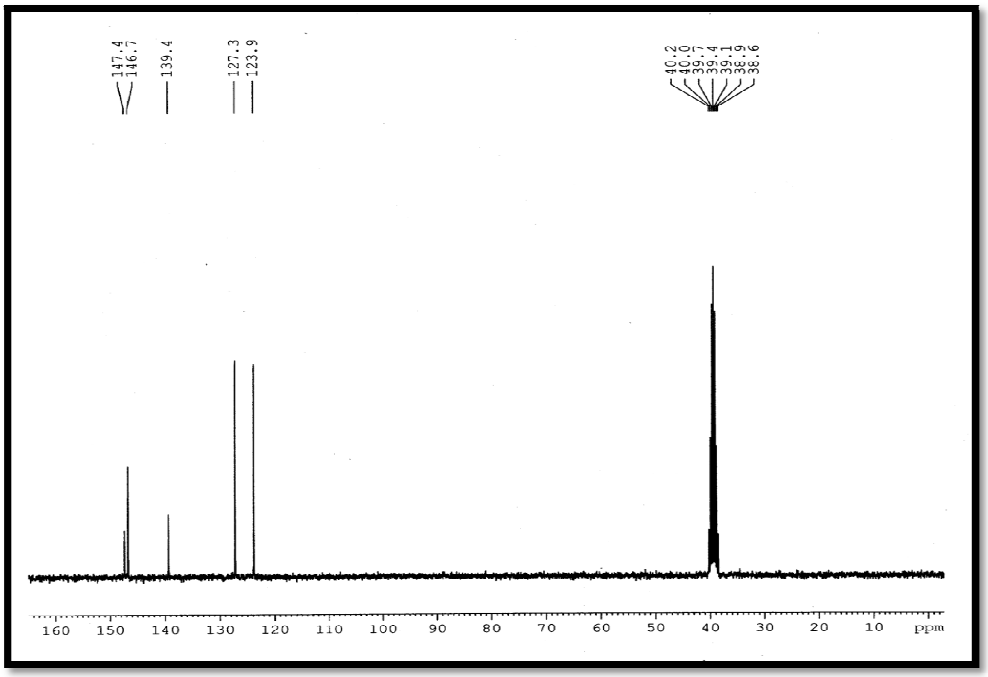


Fig.III.B.6. ^{13}C NMR spectrum of 4-Nitro benzaldoxime

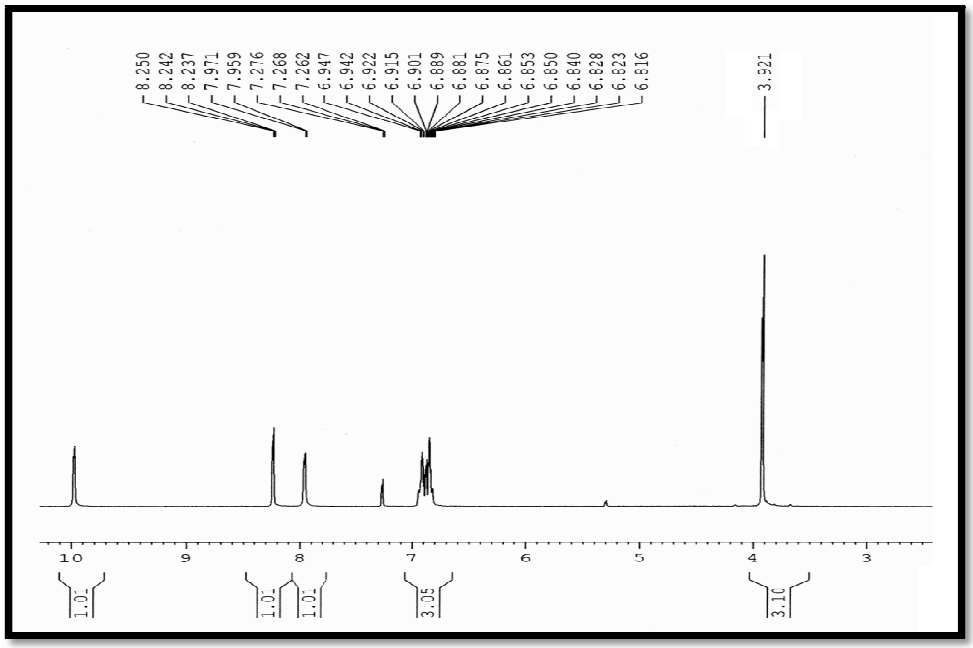


Fig.III.B.7. ^{1}H NMR of 2-Hydroxy-3-methoxy benzaldoxime

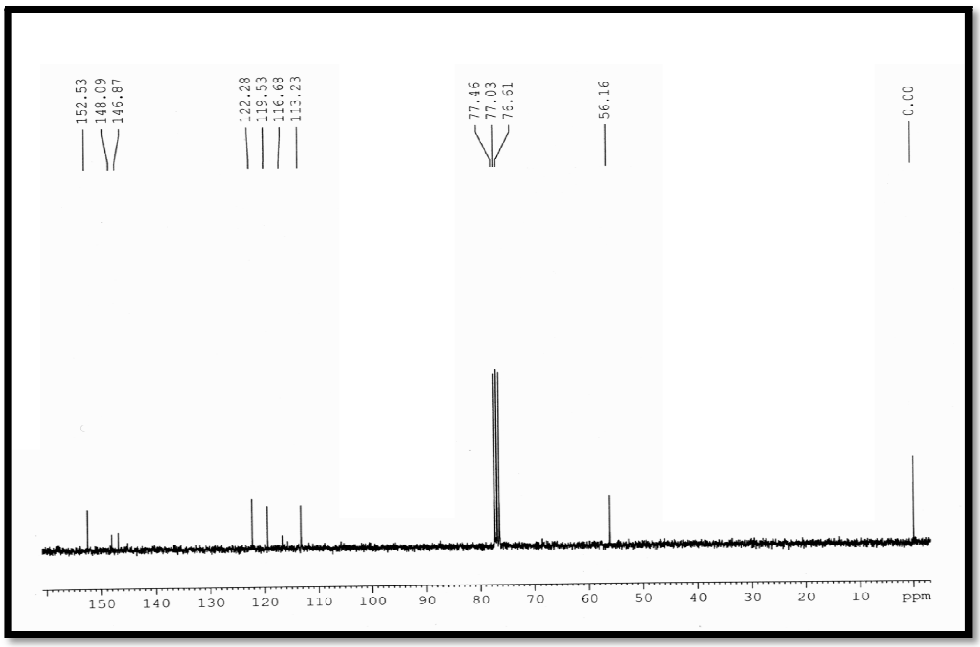


Fig.III.B.8. ^{13}C NMR of 2-Hydroxy-3-methoxy benzaldoxime

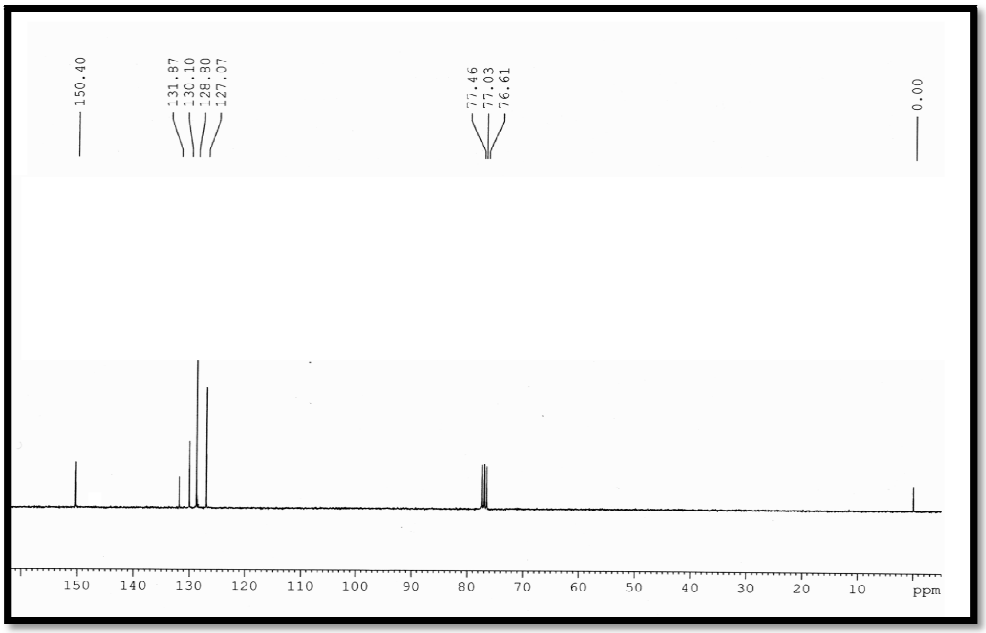


Fig.III.B.9. ^{13}C NMR of benzaldoxime

III.B.7. References

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CHAPTER-IV

$FeCl_3$ mediated one-pot transformation of aldehydes into nitriles

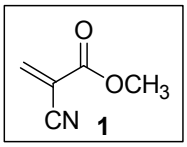
CHAPTER-IV

SECTION-A

IV.A. A brief review on nitriles, synthesis and its applications

IV.A.1. Nitrile

A nitrile is any organic compound that has –CN functional group and organic compound containing multiple nitrile groups are known as cyanocarbon. The inorganic compound containing the –CN group are not called nitriles, but cyanide instead. Nitriles are important intermediates for the syntheses of amides, amines, carboxylic acids, and esters. Nitrile are found in many valuable compound including methyl cyanoacrylate (**1**) **(fig.IV.A.1.)** used in super glue, a nitrile containing polymer used in latex free laboratory and medical gloves simply called nitrile gloves.



1

Fig.IV.A.1. Methyl cyanoacrylate

Nitrile gloves is used in the automotive and aeronautical industry to make fuel and oil handling hoses, seals, and grommets, since ordinary rubbers cannot be used. It is used in the nuclear industry to make protective gloves. Nitrile butadiene is also used to create moulded goods, footwear, sealants, sponges, expanded foams, and floor mats.

IV.A.2.Natural occurance of organo nitriles

Cyanides are produced by certain bacteria, fungi, algae and are found in a number of plants. Cyanides are found in substantial amounts in certain seeds and fruit stones, e.g., those of apricots, apples, and peaches. In plants, cyanides are usually bound to sugar molecules in the form of cyanogenic glycosides (**2**) **(fig.IV.A.2.)** (amygdalin skeleton) and defend the plant against herbivores. Cassava roots (also called manioc), an important potato-like food grown in tropical countries (and the base from which tapioca is made), also contain cyanogenic glycosides.

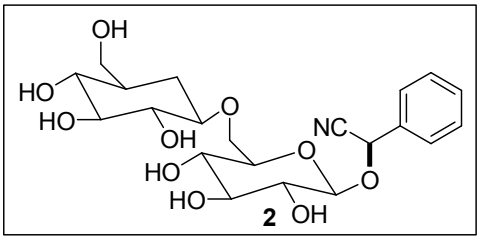


Fig.IV.A.2. Cyanogenic glycosides

IV.A.3. Structure of nitriles

The -C-N skeleton is linear in nitrile, reflecting the *sp*-hybridization of triple bonded carbon. The C-N distance is short at 1.16 ^{o}A. Nitrile is polar, as indicated by high dipole moment.

IV.A.4. Discovery of organo nitriles

The first compound of the homolog row of nitrile, the nitrile of formic acid or hydrogen cyanide was first prepared by C.W. Scheele in 1782. Later on in 1811 J. L. Gay-Lussac was able to prepare the very toxic and pure acid. The nitrile of benzoic acids was first prepared by Friedrich Wöhler and Justus von Leibig, but due to low yield, neither physical nor chemical properties were determined. In 1834 Théophile-Jules Pelouze synthesized propionitrile suggesting it to be ether of propionic alcohol and hydrocyanic acid. The synthesis of benzonitrile by Hermann Fehling in 1844, was the first method yielding sufficient substance for chemical research. He determined the structure by comparing it to the already known synthesis of hydrogen cyanide by heating ammonium formate to his result. Hermann Fehling coined the name nitrile for the newfound substance, which became the name for this group of the compounds.

IV.A.5. Biological importance of organo nitriles

Nitriles are pharmaceutically and biologically important class of compound. Over 30-nitriles containing pharmaceuticals are prescribed for a diverse variety of medical indications with more than 20-additional nitrile-containing leads in clinical development. For example (**fig.IV.A.3.**), vildagliptin (**3**) is amino-nitrile containing antidiabetic drug in which the nitrile bearing carbon is not fully substituted, citalopram (**4**) is an antidepressant drug, letrozole (**5**) and fedrozole (**6**) are the aromatase inhibitor for the treatment of breast cancer.[1]

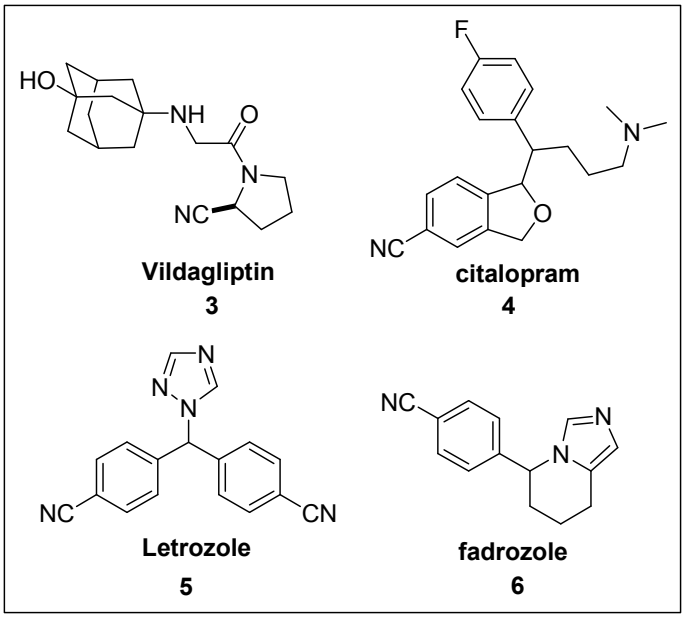
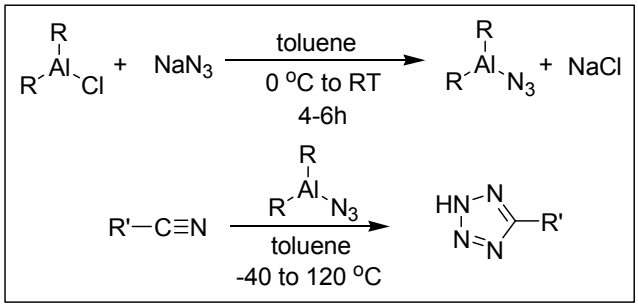


Fig.IV.A.3. Biologically potent nitrile drugs

IV.A.6. Application of nitriles in organic synthesis

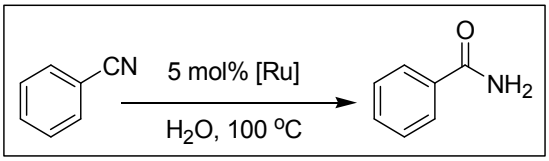
Nitriles are useful precursor for the synthesis of wide range of nitrogen containing heterocyclic compounds, such as preparation of substituted pyridine derivatives from two different alkynes and a nitrile using zirconocene and nickel complexes reported by Tamotsu Takahashi et al.[2], single-step synthesis of pyrimidine derivatives,[3] synthesis of 3, 5-diaryl-1, 2, 4-thiadiazoles from aryl nitriles in 1-butyl-3-methylimidazolium bromide promoted by $(NH_4)_2S$ and (2, 4, 6-trichloro-1, 3, 5-triazine) TCT–DMSO,[4] synthesis of highly functionalized pyridines by cyclotrimerization of one nitrile with two alkynes in the presence of water-soluble cobalt(I) catalyst in the aqueous media,[5] synthesis of 5-substituted 1*H*-tetrazoles through 1,3-dipolar cycloaddition of boron-azides and nitriles,[6] preparation of 2-substituted pyrrolidines from commercially available nitriles,[7] the Ni(0)-catalyzed the synthesis of variety of pyridines by intermolecular dehydrogenative [4 + 2] cycloaddition reaction of 1,3-butadienes with nitriles,[8] $AgNO_3$ catalyzed synthesis of 5-substituted-1*H*-tetrazole via [3+2] cycloaddition of nitriles and sodium azide in refluxing DMF.[9]

$Cu_2(OTf)_2$-catalyzed and microwave-controlled preparation of tetrazoles from nitriles and organic azides[10], synthesis of 5-substituted tetrazole from organoaluminium azide and nitrile via 1, 3-dipolar cycloaddition[11] (**scheme.IV.A.1.**), synthesis of tetrazole-tethered *C*-glycosyl α-amino acids[12], ruthenium-catalyzed single-step amide synthesis from alcohol and nitrile.[13]



Scheme.IV.A.1. Synthesis of 5-substituted tetrazole from organoaluminium azide and nitrile via 1, 3-dipolar cycloaddition

Nitriles are equally important for functional group transformation and synthesis of many valueable reagents. Many researchers reported functional group transformation by taking nitrile as starting material which includes synthesis of tertiary alkyl amines from their corresponding alkyl nitriles in the presence of a heterogeneous palladium catalyst and a source of dihydrogen in aprotic solvents,[14] selective hydration of aromatic and aliphatic nitriles with Ru(II)-phosphaurotropine catalysts[15] (**scheme.IV.A.2.**), synthesis of carboxylic acids from nitriles using recyclable ionic liquid [bmim]HSO_4 under mild condition,[16] chemoselective reduction of nitriles into aldehydes using 1, 1, 3, 3-tetramethyldisiloxane (TMDS)/triisopropoxyvanadium(V) oxide reducing system,[17] synthesis of nitrile functionalized pyridinium ionic liquids and their application in suzuki and stille carbon-carbon coupling reactions.[18]

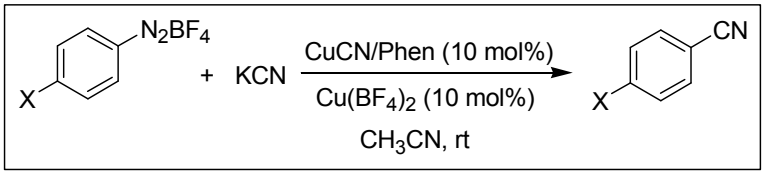


Scheme.IV.A.2. Ru(II)-phosphaurotropine catalyzed conversions of benzonitrile into benzamide

IV.A.7. Classical methods for the synthesis nitriles

IV.A.7.1. Sandmeyer reaction

In this reaction the aromatic diazonium salt react with cuprous cyanide to yield aryl nitrile. Irina P. Beletskaya et al.[19] (**scheme.IV.A.3.**) reported Cu(I)/Cu(II) catalysed synthesis of aryl nitriles by the reactions of aryl diazonium salts with KCN. As inorganic cyanides are generally used in Sandmeyer reaction for nitriles synthesis, the high toxicity of the reagent and less selectivity of the reaction makes Sandmeyer reaction not much useful synthetic route to organonitriles.

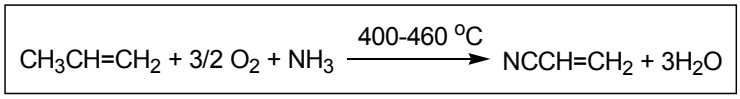


Scheme.IV.A.3. Cu(I)/Cu(II) catalyzed synthesis of nitrile from aryl diazonium salts and KCN

IV.A.7.2. Ammoxidation

The reaction of ammoxidation[20] refers to the interaction of ammonia with a hydrocarbon partner (alkene, alkane or aromatic) in the presence of oxygen and suitable catalyst. The first commercial plant built by Sohio (now BP International) used a catalyst based on Bi_2O_3.MoO.

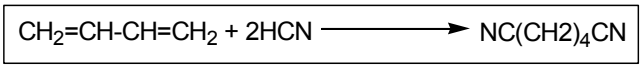
The catalyst should be multifunctional and possess redox properties. The most commonly employed contain molybdenum or antimonium oxides mixed with transition metals, such as Fe, Ni, Co and V, activated by alkali and rare-earth elements. In ammoxidation, a hydrocarbon is partially oxidised in the presence of ammonia. This conversion is practised on a large scale for acrylonitrile (**scheme.IV.A.4.**). The major side in this reaction is acetonitrile. Most of the derivative of benzonitrile, pthalonitrile as well as isobutyronitrile is prepared by ammoxidation. The process is assumed to proceed via aldehyde.



Scheme.IV.A.4. Synthesis of acrylonitrile from propene

IV.A.7.3. Hydrocyanation

Hydrocyanation[21] is a process for the synthesis of nitrile from alkene and hydrogen cyanide. The addition of hydrogen cyanide across activated carbon-carbon π bonds, such as the C=C bond of α, β-unsaturated carbonyl compounds, is a well-known, synthetically useful transformation. Because this process requires a sufficiently electrophilic substrate, unactivated alkenes will not undergo addition under conditions useful for activated substrates. However, the addition of hydrogen cyanide across a π bond is a thermodynamically favorable process, and the high activation barriers associated with addition to unactivated alkenes and alkynes may be surmounted using transition-metal catalysis. Transition-metal catalyzed addition of cyanide across π bonds may occur in a Markovnikov or anti-Markovnikov fashion to provide fully saturated nitriles or vinyl nitriles. The most common catalysts used to effect hydrocyanation are nickel(0) and palladium(0) complexes. The industrial development of nickel-catalyzed hydrocyanation, which produced several concepts useful to the field of organometallic chemistry, was motivated by the need to mass-produce adiponitrile (1,4-dicyanobutane) for nylon synthesis. The most important industrial application is the nickel-catalyzed synthesis of adiponitrile (NC–$(CH_2)_4$–CN) synthesis from 1, 3–butadiene (CH_2=CH–CH=CH_2) (**scheme.IV.A.5.**). Adiponitrile is a precursor to hexamethylenediamine (H_2N–$(CH_2)_6$–NH_2), which is used for the production of certain kinds of nylon.

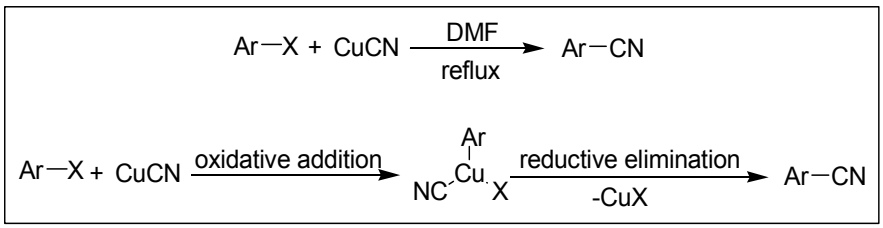


Scheme.IV.A.5. Synthesis of adiponitrile from 1,3 butadiene

IV.A.7.4. Rosenmund–von Braun reaction

Aryl nitriles can be prepared by the cyanation of aryl halides with an excess of copper(I) cyanide in a polar high-boiling solvent such as DMF, nitrobenzene, or pyridine at reflux temperature is called Rosenmund–von Braun reaction.[22] The mechanism probably

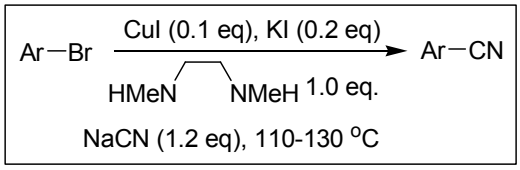
involves the formation of a Cu(III) species through oxidative addition of the aryl halide. Subsequent reductive elimination then leads to the formation of product (**scheme.IV.A.6.**).



Scheme.IV.A.6. Synthesis of aryl nitrile from aryl halide and CuCN under reflux condition

The cyanation of aryl bromides requires extreme reaction conditions (150-280 °C) which may not be compatible with sensitive substrates. This is a serious limitation of Rosenmund–von Braun reaction. In addition, the stoichiometric amount of copper(I) cyanide which is utilized in the reaction may complicate the separation of the nitrile products from the copper halide salts produced in the reaction. When used on the industrial scale, the stoichiometric amounts of the copper salts also present a significant waste disposal problem.

The excess of copper cyanide and the use of a polar, high-boiling point solvent, very high temperature makes the classical method purification less applicable for the synthetic and industrial area. More recently, copper-catalyzed domino halide exchange-cyanation of aryl bromides was reported by Stephen L. Buchwald et al.[23] where the improvement of traditional Rosenmund-von Braun reaction is described. The reaction conditions are much milder, and the use of stoichiometric amounts of copper(I) cyanide and polar solvents is avoided; therefore, the isolation and purification of the nitrile products is greatly simplified. In addition, this method exhibits excellent functional group compatibility (**scheme.IV.A.7.**).

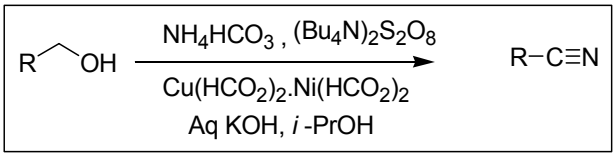


Scheme.IV.A.7. Copper-catalyzed cyanation of aryl bromides

IV.A.8. Modern methods for the synthesis of nitriles from various functional groups

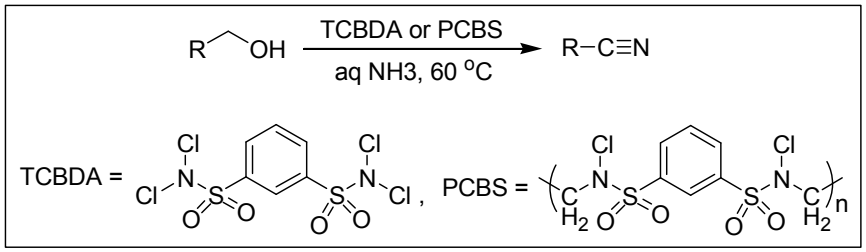
IV.A.8.1.Synthesis of nitriles from alcohols

Fen-Er Chen et al.[24] (**scheme.IV.A.8.**) reported one-pot method for the synthesis of nitriles from the corresponding primary alcohols by nickel-catalyzed oxidation with tetrabutylammonium peroxydisulfate in the presence of ammonium hydrogen carbonate under basic aqueous conditions and the method is applicable to aliphatic, aromatic and heterocyclic nitriles in excellent yields.



Scheme.IV.A.8. One-pot transformation of primary alcohols into nitriles

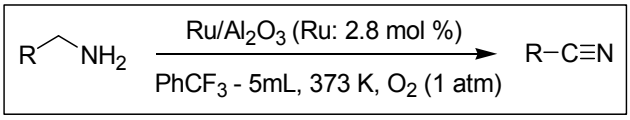
The applications of poly(*N*, *N*′-dichloro-*N*-ethylbenzene-1, 3-disulfonamide) (PCBS) and *N*, *N*, *N*′, *N*′-tetrachlorobenzene-1, 3-disulfonamide (TCBDA) for the preparation of nitriles by the direct oxidative conversion of primary alcohols was successfully carried out with TCBDA and PCBS in aqueous ammonia was reported by Ramin Ghorbani-Vaghei et al.[25] (**scheme.IV.A.9.**).



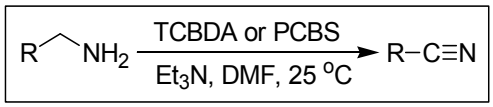
Scheme.IV.A.9. One-pot transformation of primary alcohols into nitriles

IV.A.8.2. Synthesis of nitriles from primary amines

Noritaka Mizuno et al.[26] (**scheme.IV.A.10.**) and Ramin Ghorbani-Vaghei et al.[5] (**scheme.IV.A.11.**) have synthesized nitriles from primary amine by direct oxidative process. Noritaka Mizuno et al. reported Ru/Al_2O_3 (1.4 wt % Ru) heterogeneous catalyst for the oxidation of non-activated, as well as activated amines to the corresponding nitriles with 1 atm dioxygen or air in trifluoro toluene as solvent. Ramin Ghorbani-Vaghei et al.[24] have reported poly(*N*, *N*′-dichloro-*N*-ethylbenzene-1, 3-disulfonamide) (PCBS) and *N*, *N*, *N*′, *N*′-tetrachlorobenzene-1, 3 disulfonamide (TCBDA) for the preparation of nitriles from primary amines in the presence of triethyl amine in DMF at 25 ^oC to furnish corresponding nitriles from primary amine.



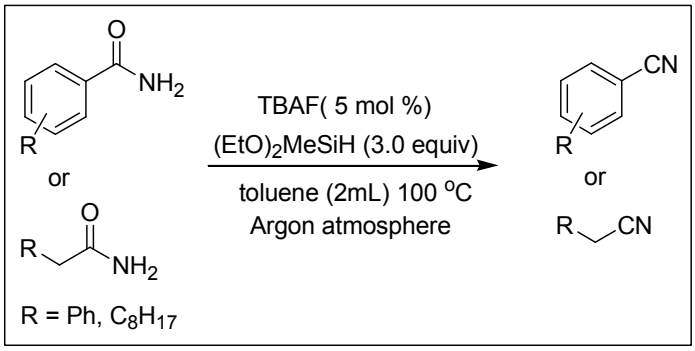
Scheme.IV.A.10. Ru/Al_2O_3 catalyzed oxidative transformation of primary amine into nitriles



Scheme.IV.A.11. Transformation of primary amine into nitrile in the presence of TCBDA or PCBS

IV.A.8.3. Synthesis of nitriles from amides

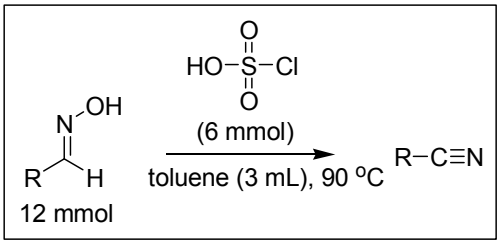
Matthias Beller et al.[27] (**scheme.IV.A.12.**) reported the synthesis of aliphatic and aromatic nitriles synthesized nitriles from amide by catalytic dehydration of aromatic and aliphatic amides using silanes in the presence of catalytic amounts of tetrabutylammonium fluoride (TBAF). The protocol proceeds with high selectivity under mild conditions.



Scheme.IV.A.12. TBAF catalyzed transformation of amide into nitriles

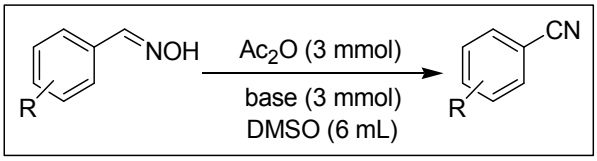
IV.A.8.4. Synthesis of nitriles from oximes and azides

The one of the alternative approach for the synthesis of nitrile is dehydration of aldoximes. Youquan Deng et al.[28] (**scheme.IV.A.13.**) reported the dehydration of aldoximes to nitriles using chlorosulfonic acid in toluene.



Scheme.IV.A.13. Transformation of oxime into nitrile in the presence of chlorosulfonic acid

The transformation of aldoximes to nitriles using acetic anhydride as dehydration agent under weak alkaline condition is reported by Guangyu Xu et al.[29] (**scheme.IV.A.14.**), which allow the conversion of a range of aldoximes including aromatic aldoximes, alphatic aldoximes, and heterocyclic aldoximes in good to excellent yields. The other interesting approach is the oxidative transformation of azide into nitrile. Noritaka Mizuno et al.[30] reported the transformation of aerobic oxidative synthesis of nitriles from primary azides with high performance heterogeneous ruthenium hydroxide catalyst $Ru(OH)x/Al_2O_3$.

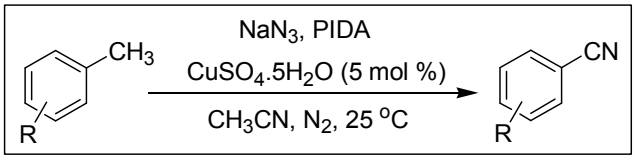


Scheme.IV.A.14. Transformation of oximes into nitriles

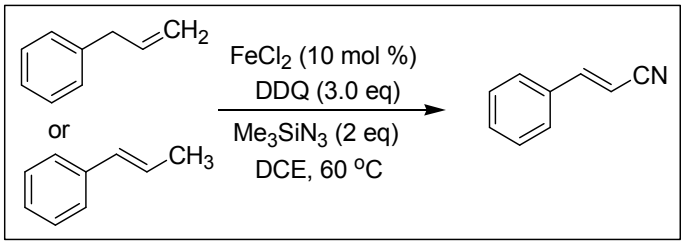
The direct oxidative rearrangement of alkenes, methyl arenes and benzyl or allyl halide are also well known in the literature. But in those cases, elongation of one carbon in parent compound takes place.

IV.A.8.5. Synthesis of nitriles from alkenes, methyl arenes and benzyl or allyl halides

The direct oxidative rearrangement of alkenes, methyl arenes and benzyl or allyl halide are also well known in the literature. But in those cases, elongation of one carbon in parent compound takes place**.** Ning Jiao et al.[31] have reported direct transformation of methyl arenes to aryl nitrile at room temperature (**scheme.IV.A.15.**).This report comprise the use of NaN_3 (2.0 mmol), PIDA (1.6 mmol), $CuSO_4.5H_2O$ (0.025 mmol) in acetonitrile (4 mL) per 0.5 mmol of reactant at room temperature. During this transformation, three C-H bond cleavages occur. This observation offer an opportunity achive C(sp^3)-H functionalization under mild condition. Later on they reported the direct approach to alkenyl nitriles from allylarenes or alkenes facilitated by an inexpensive homogeneous iron catalyst[32] by taking Me_3SiN_3 (1.0 mmol), $FeCl_2$ (0.05 mmol), DDQ (1.5 mmol) in dry DCE (2 mL) per 0.5 mmol of reactant with stirring at 60 °C under air where a series of alkenyl nitrile were prepared **(scheme.IV.A.16.)**.

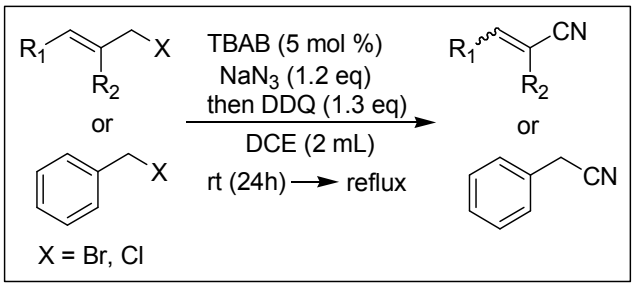


Scheme.IV.A.15. Transformation of methyl arenes to aryl nitriles



Scheme.IV.A.16. Synthesis of alkenyl nitriles from alkenes and allyl arenes

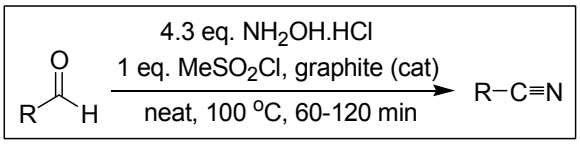
In continuation of their finding, Ning Jiao et al explore their finding for the synthesis of aryl or alkenyl nitriles from benzyl and allyl halides by TBAB-catalyzed substitution and the subsequent oxidative rearrangement[33] (**scheme.IV.A.17.**). A wide range of aryl and alkenyl nitrile was prepared to show the general applicability of the protocol.



Scheme.IV.A.17. Transformation of benzyl and allyl halides to aryl and alkenyl nitriles

IV.A.8.6. Synthesis of nitriles from aldehydes

The transformation of carbonyls into nitriles using hydroxyl amine is an attractive alternative approach for the synthesis of nitriles without elongation of carbon chain in parent compound. In the last decade numbers of protocols have been developed for the synthesis of nitriles from aldehydes by using diverse catalytic systems. Hashem Sharghi et al. reported graphite catalyzed one-step conversion of aldehydes into nitriles in dry media[34] where a variety of aryl, heteroaryl and alkyl nitrile were synthesized in a good to excellent yield (**scheme.IV.A.18.**).



Scheme.IV.A.18. Graphite catalyzed one-step conversion of aldehydes into nitriles

Propylphosphonic anhydride (**fig.IV.A.4.**) also found to be a remarkably efficient reagent for the one-pot transformation of aromatic, heteroaromatic, and aliphatic aldehydes to nitriles[35],

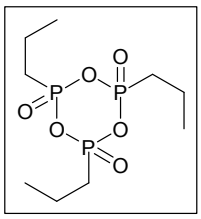
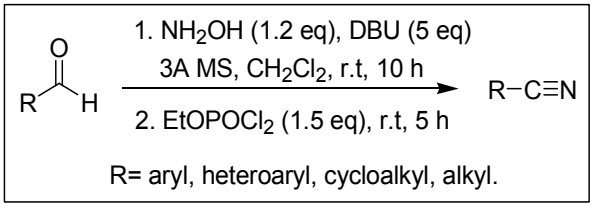


Fig.IV.A.4. Propylphosphonic anhydride

K. Rajender Reddy et al reported non-transition metal catalyzed oxidative conversion of aldehydes to corresponding nitriles in excellent yields whic was achieved by the catalytic amount of KI or I_2 in combination with TBHP as an external oxidant.[36] The reaction of carbamoylated hydroxylamine with aromatic aldehydes in THF or in toluene under refluxing condition affords the corresponding nitriles.[37] Shlomo Rozen et al. reported the transformation of aldehydes into nitrile via N, N-dimethylhydrazones formation which undergo a rapid oxidative cleavage to form nitriles in very high yields on reaction with $HOF.CH_3CN$ under mild conditions.[38] Jia-Liang Zhu et al.[39] reported the one-pot conversion of various aldehydes into the corresponding nitriles where ethyl dichlorophosphate/DBU used for the dehydration of aldoxime intermediates to effect the transformation (**scheme.IV.A.19.**).

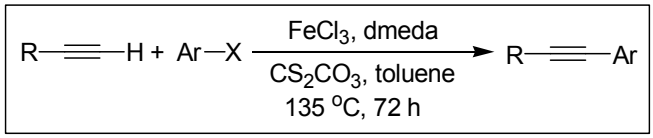


Scheme.IV.A.19. One-pot conversion of aldehydes into nitriles

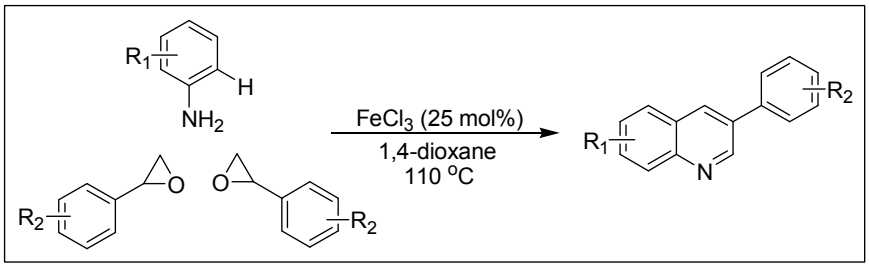
IV.A.9. Application of iron salts in organic transformations

Transition metal salts are essential instruments in the toolbox of the organic chemists. The current requirements for clean, fast, efficient, and selective processes have increased the demand for such metal-based reaction promoters, especially the ones that

can be applied in small or catalytic amounts. However, many catalysts are derived from heavy or rare metals and their toxicity and prohibitive prices constitute severe drawbacks for large-scale applications. In contrast, iron is one of the most abundant metals on earth, and consequently one of the most inexpensive and environmentally friendly ones. Moreover, many iron salts and complexes are commercially available. However, the last few years have seen a rise of its use, and some very efficient processes able to compete with other metal-catalyzed organic transformation. The high catalytic activity and functional group tolerance, low toxicity, and inexpensiveness make iron salt a versatile reagent and have gained special attention in modern organic chemistry such as oxidative radical cross coupling[40] which is important powerful reaction for carbon-carbon and carbon heteroatom bond formation, Sonogashira coupling reaction between terminal alkyne and aryl or hetero aryl iodide[41] (**scheme.IV.A.20.**), -OH selective Prins cyclization where the library of 4-OH-tetrahydropyrans were synthesized stereoselectively,[42] iron III chloride activated oxidation of alkanes by nitridoosmate $[Os(N)O_3]^-$ to corresponding alcohols, ketones and chloro derivatives[43], synthesis of polysubstituted benzofuran from the reaction of phenol and *β*-keto ester which is one of the important structural units and widely found in heterocyclic compounds of biological and medical importance,[44] synthesis of series of substituted quinolines from N-aryl-N-(2-alkynyl)toluenesulfonamides via intramolecular cyclization and concomitant detosylation,[45] synthesis of quinoline derivatives by tandem reaction of aniline with styrene oxide via C-C cleavage and C-H activation[46] (**scheme.IV.A.21.**), synthesis of variety of 3-functionalized benzo[*b*]furans intramolecular cyclization of electron-rich α-aryl ketones,[47] intramolecular *O*-arylation reaction and the synthesis of benzoxazole derivatives, starting from the readily available 2-haloanilines,[48] addition of electron rich arenes to aryl substituted alkynes to form 1,1-diaryl alkene via C-C bond forming reaction,[49] synthesis of amide from benzylic alcohols and nitriles using Ritter reaction,[50] Friedel–Crafts alkylation reaction for the synthesis of benzyl arenes from benzyl ethers,[51] one-pot three-component aza-Friedel Crafts reactions of indoles, aldehydes, and tertiary aromatic amines for the synthesis of 3-diarylmethyl indoles,[52] Pinacol-pinacolone rearrangement of benzopinacols.[53]

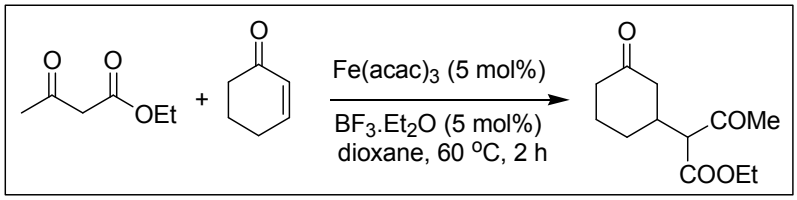


Scheme.IV.A.20. Iron-catalyzed Sonogashira coupling of terminal alkynes with aryl iodides



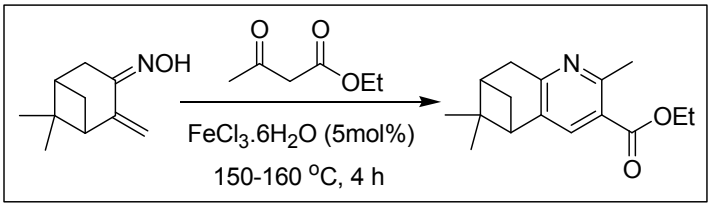
Scheme.IV.A.21. Iron-promoted synthesis of quinolines

Pavel Kočovaký et al.[54] have reported the use of Iron (III) acetylacetonate as homogeneous catalyst for the Michael addition of ethyl acetoacetate to cyclohexenone. Michael addition is one of the most useful methods for the mild formation of C–C bonds. (**scheme.IV.A.22.**)



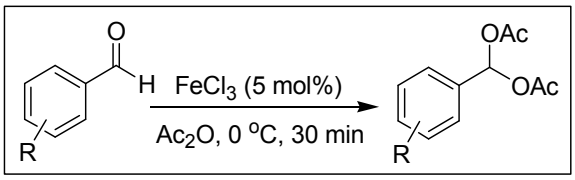
Scheme.IV.A.22. Iron catalyzed michael addition of β-dicarbonyls

The reaction of α, β-unsaturated oximes with ethyl acetoacetate in the presence of $FeCl_3.5H_2O$ resulted in Michael addition followed by ring closure to produce substituted nicotinic acid derivatives in a very efficient way (**scheme.IV.A.23.**).[55]



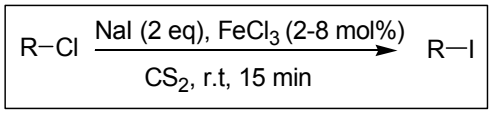
Scheme.IV.A.23. Iron catalyzed syntheisi of nicotinic acid derivatives via Michael addition pathway

A transformation related to the acetalyzation is the conversion of carbonyls into geminal diesters, or acylals, which can be preferred to acetals as protecting groups due to their superior stability in neutral and basic media. In this case, anhydrous $FeCl_3$ has been shown to be very efficient in catalyzing the reaction. Thus, acylals of various aldehydes could be prepared by reaction with acetic anhydride under mild conditions[56] (**scheme.IV.A.24.**).

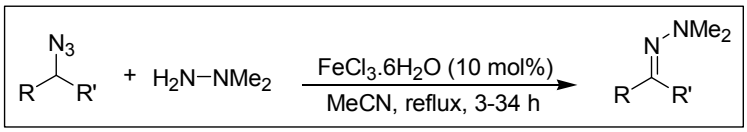


Scheme.IV.A.24. Conversion of aldehydes into geminal diacetates

Iron(III) chloride has been widely used as Lewis acid for electrophilic aromatic substitutions. The Friedel-Crafts reaction have been the most studied reactions. Synthesis of substituted indenes through the $FeCl_3.6H_2O$-catalyzed intramolecular Friedel-Crafts cyclization of aryl-substituted allylic alcohols.[57]Iron complexes have also been used to prepare iodo compounds from the corresponding chlorinated substrates (Finkelstein reaction). This reaction is performed in carbon disulfide or benzene at room temperature with 2 equiv of sodium iodide and gives rise to excellent yields of products (>95%) in a few minutes[58] (**scheme.IV.A.25.**). Iron trichloride has been used in the substitution of azide by dimethyl hydrazine, which allows the formation of hydrazones in very good yields[59] (**scheme.IV.A.26.**).



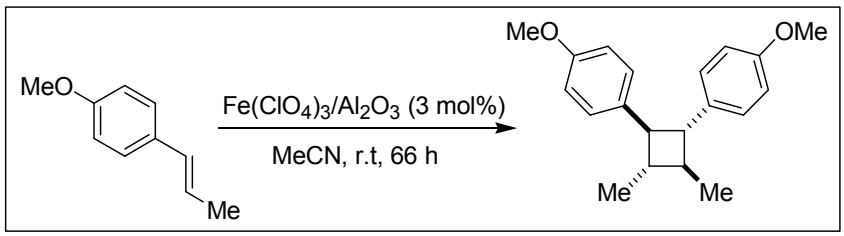
Scheme.IV.A.25. Iron catalyzed synthesis of alkyl iodides from alkyl chlorides



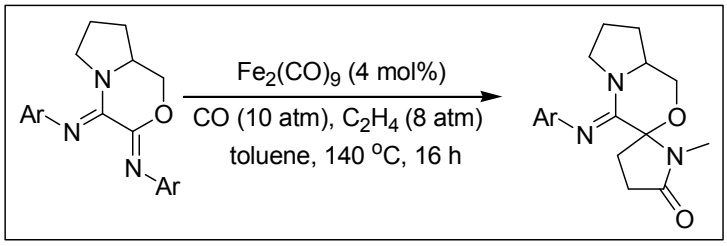
Scheme.IV.A.26. Synthesis of hydrazones from azides

IV.A.10. Application of iron salts in cycloaddition reactions

A cycloaddition is a pericyclic chemical reaction, in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity. Cycloaddition reaction of unsaturated molecule is very powerful tools for the synthesis of cyclic products. The [2+2] cyclodimerization of *trans*-olefin can be performed using $Fe(ClO_4)_3$ under air. Best results are obtained with a catalyst supported on aluminium oxide (3 mol %) affording exclusively the C_2-symmetric cyclobutane in 92% yield (**scheme.IV.A.27.**).[60] A single example of a hetero-Pauson-Khand-type [2+2+1] cycloaddition reaction of a ketimine, carbon monoxide, and ethylene has been reported by Imhof et al.[61]Only one of the two imine moieties is activated, and the reaction leads to the formation of pyrrolidinone derivatives (55%) (**scheme.IV.A.28.**).



Scheme.IV.A.27. [2+2]-cycloaddition reaction of styrene derivatives using an Fe(III) salt catalyst



Scheme.IV.A.28. [2+2+1] cycloaddition reaction of ketimines, carbon monoxide and ethylene

[2+2+2] cyclotrimerization alkynes is catalyzed by iron(0) complexes, and leads to polysubstituted aromatic rings.[62] Iron salts are equally efficient and important for catalyzing [4+2] cycloaddition,[63] [4+4] cycloaddition[64] and 1, 3-dipolar cycloaddition.[65]

IV.A.11. Conclusion

Nitriles are not only biologically important but also are useful organic intermediate for the functional group transformations and synthesis of nitrogen containing heterocyclic compound. Various catalytic system have been reported for the synthesis of this intermediate from different functional group. Based on the literature review, it appeared that most of the reported methodologies suffer from one or more draw-backs such as long reaction time, use of strong oxidant and expensive catalyst, lack of straight-forward process. Therefore, author felt necessary to develop a simple and low-cost protocol by using inexpensive and environmentally benign metal salt for the one-pot synthesis of nitriles.

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CHAPTER-IV

SECTION-B

$FeCl_3$ mediated one-pot transformation of aldehydes into nitriles

IV.B. Present Investigation

IV.B.1. Background of the present investigation

Nitriles are industrially important intermediate for the production of agrochemicals, pharmaceutical, polymers, dyes and pigments.[1] In addition, they serve as potential synthon for the functional group transformation[2] and heterocyclic synthesis.[3] Classical methods for the nitrile synthesis comprises Sandmeyer reaction,[4] ammoxidation of aldehydes,[5] Kolbe nitrile synthesis,[6] hydrocyanation of alkenes[7] and Rosenmund-von Braun reaction.[8] During the last decades, use of various catalytic systems have been established for the oxidative transformation of nitrile from the substrates like alcohols,[9] amines,[10] amides,[11] oximes,[12] and azides.[13] The direct oxidative rearrangement of alkenes,[14] methyl arenes[15] and benzyl or allyl halides[16] into nitrile are also known but in such cases elongation of one carbon in parent compound takes place. The transformation of carbonyl to nitriles using hydroxyl amine is an alternative attractive approach without elongation of carbon chain. The literature survey reveals that a host of catalytic systems were applied for the one-pot transformation of aldehydes into nitriles.[17] Although a plethora of synthetic strategies have been developed, the use of expensive catalyst, various oxidants, prolong reaction time, hazardous metal salts, work-up difficulties made the various existing methodologies non desirable under the aspect of sustainable synthesis. Because of wide application of nitriles as a potent bioactive material[18] as well as synthon for designing the molecules, there is demand for less expensive, straightforward and environmentally friendly protocols for their synthesis.

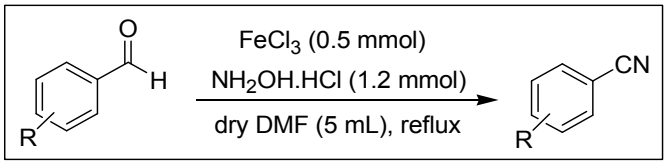
It is well documented[19] that iron is one of the most versatile highly abundant transition metal which is environmentally benign, low toxic and inexpensive. it plays key roles in fundamental biological processes and remarkable roles in wide area of organic synthesis.[20] Being a Lewis acid and mild oxidising agent, iron III chloride can easily form an adduct with Lewis bases and thereby activate organic substrates. The high catalytic activity and functional group tolerance, low toxicity and inexpensiveness

makes iron salt a versatile reagent and have gained special attention in modern organic chemistry, such as oxidative radical cross-coupling,[21] Sonogashira reactions of terminal alkynes and aryl halides,[22] Prins cyclization,[23] catalytic oxidation of alkane,[24] heterocyclic synthesis by C-H, C-X bond activation and condensation,[25] alkenylation of arenes,[26] synthesis of amide,[27] Friedel-Crafts reaction,[28] Aldol reactions,[29] and pinacol-pinacolone rearrangement.[30] Behbahani et al. and Desai et al. have already reported the use of iron III salt for the transformation of oximes to nitriles.[31] However, to the best of our knowledge, the direct transformation of carbonyl to nitrile using hydroxylamine hydrochloride by iron III chloride as a sole mediator has never been reported so far. With these backgrounds of iron salt, and in view of our present attempt to search for a milder reaction condition coupled with use of environment-friendly, cost efficient, high functional group tolerance and high yielding reagent for nitrile synthesis, author felt necessary to develop a general reaction protocol for the one step transformation of aldehydes to nitriles and have chosen ferric chloride as ideal reagent for the present investigation to meet the demand for the sustainable development.

IV.B.2. Results and discussion

In an endeavour to start our present investigation we have chosen vanillin as our model compound for the desired transformation. The model reaction comprising vanillin (1 mmol), hydroxylamine hydrochloride (1.5 mmol) and ferric chloride anhydrous (1 mmol) at room temperature furnished only aldoxime instead of nitrile. We started raising the reaction temperature when only trace amount of nitrile was formed at 100 ^{o}C. The reaction was then set up under reflux condition when it was found to yield the corresponding nitrile by more than 90% in 3 h. Finally we could optimize the quantity of reactants as 1.2 mmol hydroxylamine hydrochloride and 0.5 mmol ferric chloride (anhydrous) per mmol of aldehyde and found 98% yield of nitrile in 3 h in DMF under reflux condition (**table.IV.B.1., entry 2**). It was also found that 5 ml solvent is sufficient for complete transformation. The similar reactions were carried out with other iron salts but found not efficient for the desired transformation. The results with other iron salts are reported in (**table.IV.B.1**). For the generalization of our scheme, the aldehydes 1-11 was treated under optimized reaction condition and the nitriles were obtained in 76-98% yields (**table.IV.B.2**). It was evident from (**table.IV.B.2**) that the aldehydes without substituent (**entry 10-11)** and having electron-donating groups like –

OMe, -OH, -N(Me)$_2$ furnished higher yield whereas aldehydes with electron-withdrawing groups (**entry 4-5)** furnished lower yield (**scheme.IV.B.1.**).



Scheme.IV.B.1. $FeCl_3$-mediated transformation of aldehydes to nitriles

Table.IV.B.1.

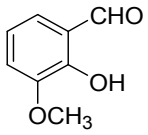
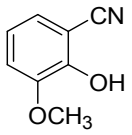
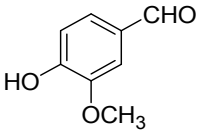
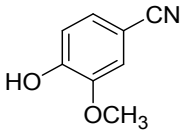
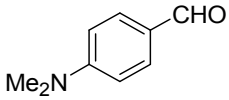
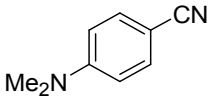
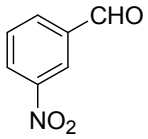
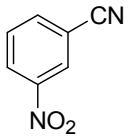
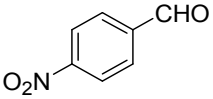
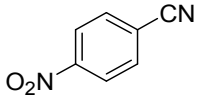
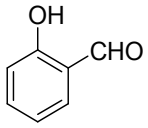
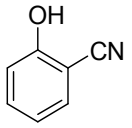
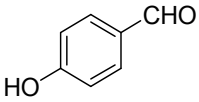
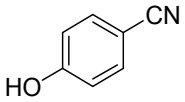
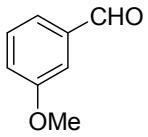
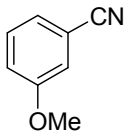
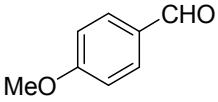
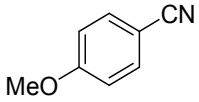
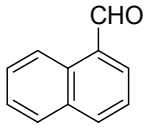
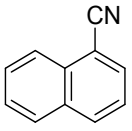
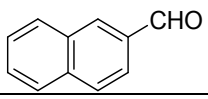
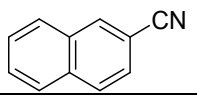
Selection of iron salts

Sl.No.	Iron salts	Time (h)	Yield %[b]
1	$FeSO_4.7H_2O$	6	15
2	$FeCl_3$	3	98[c]
3	$FeCl_2.4H_2O$	7	32
4	$Fe(NO_3)_3.9H_2O$	7	26
5	$Fe(OTf)_3$	4	65
6	$(NH_4)_2Fe(SO_4)_2.6H_2O$	5	30
7	$NH_4Fe(SO_4)_2.12H_2O$	7	38

[a]Reaction of vanillin (1 mmol), hydroxylamine hydrochloride (1.2 mmol) and iron salt (0.5 mmol) in 5ml dry DMF under reflux condition. [b]isolated yield. [c]anhydrous iron (III) chloride found superior among other salts.

Table.IV.B.2.

$FeCl_3$-mediated transformation of aldehydes to nitriles

Entry	Aldehydes	Time (h)	Product	Yield%[b]
1		3		98
2		3		98
3		4.5		95
4		4		79
5		5		76
6		4		96
7		4		98
8		4		97
9		4		98
10		4		96
11		4		97

[b]Isolated Yield.

IV.B.3 Experimental

IV.B.3.1. Chemicals

All the chemicals which were used for the present investigation are listed in the **table.IV.B.3.** The details of the chemicals regarding their source and purity are summarised in **table.IV.B.3.**

Table.IV.B.3.

Chemicals used for the present investigation

Entry	Chemical	Source	Purity (%)
1	2-Hydroxy-3-methoxybenzaldehyde	ACROS	99
2	3-Methoxy-4-hydroxybenzaldehyde	S.D Fine	99
3	N,N-dimethyl-4-aminobenzaldehyde	Sigma-Aldrich	99
4	3-Nitrobenzaldehyde	LOBA Chemie	98
5	4-Nitrobenzaldehyde	LOBA Chemie	99
6	2-Hydroxybenzaldehyde	S.D Fine	99
7	4-Hydroxybenzaldehyde	S.D Fine	98
8	3-Methoxybenzaldehyde	Chemical Book	97
9	4-Methoxybenzaldehyde	Sigma-Aldrich	98
10	1-Napthaldehyde	Sigma-Aldrich	95
11	2-Napthaldehyde	Sigma-Aldrich	98
12	Hydroxylamine hydrochloride	Fisher Scientific	96
13	Ferric chloride	Sigma-Aldrich	99.99
14	Sodium sulphate anhydrous	SRL	99.5
15	DMF	Merck	98
16	Petroleum ether	Thomas Baker	98
17	Ethyl acetate	Thomas Baker	99
18	Silica gel 60-120 mesh for column	SRL	-
19	Silica gel for TLC	SRL	-
20	Potassium bromide for FT IR	Merck	99
21	$CDCl_3$ for NMR	ACROS	99.8
22	DMSO-d_6 for NMR	SRL	99.8

IV.B.3.2. Reaction procedure and purification

Aldehyde (1 mmol) and hydroxylamine hydrochloride (1.2 mmol) were added successively to a solution of anhydrous ferric chloride (0.5 mmol) in 5 ml dry DMF. The mixture was reflux for appropriate time (**table.IV.B.2**). The progress of the reaction was monitored by TLC. After completion of the reaction, the solution was poured into 100 ml water and extract with ethyl acetate washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate (96:4) as eluent to afford the pure nitriles.

IV.B.3.3. Spectroscopic measurements

IR spectra were recorded on KBr disks and nujol in the range 4000-400 on Perkin Elmer FT IR spectrometer.^{1}H NMR were recorded on 300 and 500 MHz and ^{13}C NMR were recorded on 75 MHz Bruker Avance FT NMR spectrometer using TMS as internal standard.

IV.B.4. Conclusion

In conclusion, the author has developed an easy and one pot route to nitrile from aldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol) and ferric chloride (0.5 mmol). Excellent yield, cost efficient, environmental benign, high functional group tolerance and simple work-up process are the added advantages of this protocol.

IV.B.5. Spectroscopic data

IV.B.5.1. 2-Hydroxy-3-methoxy-benzonitrile

IR (cm^{-1}, neat): 3351 (-OH), 2231 (-CN), 1611, 1591, 1492, 1070, 730. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.92 (s, 3H), 6.32 (s, 1H), 6.87-6.9 (m, 1H), 7.02-7.04 (m, 1H), 7.09 (d, 1H, J=7 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 56.3, 98.6, 114.6, 115.9, 120.4, 123.9, 146.7, 148.9 ppm.

IV.B.5.2. 4-Hydroxy-3-methoxy-benzonitrile

IR (cm^{-1}, KBr): 3388 (-OH), 2227 (-CN), 1605, 1591, 1517, 1028, 819, 616. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.93 (s, 3H), 6.1 (s, 1H), 6.96 (d, 1H, J=10 Hz), 7.08 (d, 1H, J=1.5 Hz), 7.22-7.26 (m, 1H) ppm. ^{13}C NMR (75 MHz,): δ, 56.4, 103.3, 113.7, 115.2, 119.2, 127, 146.6, 149.9 ppm.

IV.B.5.3. 4-*N,N*-dimethylamino-benzonitrile

IR (cm^{-1}, KBr): 2909, 2211 (-CN), 1608, 1527, 1371, 1173, 818. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.04 (s, 6H), 6.69 (d, 2H, J=15 Hz), 7.48, (d, 2H, J=15 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 39.9, 97.4, 111.4, 120.6, 133.4, 152.5 ppm.

IV.B.5.4. 3-Nitro-benzonitrile

IR (cm^{-1}, KBr): 3080, 2238 (-CN), 1618, 1534, 1356, 1102, 735. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.71-7.76 (m, 1H), 7.98-8.01 (m, 1H), 8.46-8.5 (m, 1H), 8.53-8.84 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 114.2, 116.5, 127.1, 127.3, 127.6, 130.6, 137.6 ppm.

IV.B.5.5. 4-Nitro-benzonitrile

IR (cm^{-1}, KBr): 3107, 2233 (-CN), 1602, 1526, 1349, 1295, 1106, 860, 682. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.88 (d, 2H, J=15 Hz), 8.35 (d, 2H, J=15 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 116.7, 118.3, 124.3, 133.4, 150 ppm.

IV.B.5.6. 2-Hydroxy-benzonitrile

IR (cm^{-1}, KBr): 3281 (-OH), 2231 (-CN), 1605, 1505, 1361, 1236, 848, 751, 668. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 6.95-7.03 (m, 2H), 7.43-7.52 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 99.5, 116.4, 120.9, 132.9, 133.2, 134.7, 158.5ppm.

IV.B.5.7. 4-Hydroxy-benzonitrile

IR (cm^{-1}, KBr): 3292 (-OH), 2234 (-CN), 1613, 1586, 1509, 1285, 1167, 838,702. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 6.14 (s, 1H), 6.91 (d, 2H, J=15 Hz), 7.55 (d, 2H, J=15.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 103.4, 116.4, 119.2, 134.2, 159.9 ppm.

IV.B.5.8. 3-Methoxy-benzonitrile

IR (cm^{-1}, KBr): 2943, 2230 (-CN), 1596, 1578, 1290, 1265, 1044, 788, 682. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 3.83 (s, 3H), 7.11-7.39 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 55.5, 113.4, 116.9, 118.7, 119.5, 124.2, 130.3, 159.4 ppm.

IV.B.5.9. 4-Methoxy-benzonitrile

IR (cm^{-1}, KBr): 2942, 2218 (-CN), 1606, 1509, 1305, 1258, 1177, 1024, 830, 683. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.85 (s, 3H), 6.94 (d, 2H, J=9 Hz), 7.58 (d, 2H, J=9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 55.5, 103.9, 114.7, 119.2, 133.9, 162.8 ppm.

IV.B.5.10. Napthalene-1-carbonitrile

IR (cm^{-1}, neat): 3061, 2222 (-CN), 1590, 1512, 1375, 1213, 801, 771. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.48-7.7 (m, 3H), 7.88-7.92 (m, 2H), 8.06 (d, 1H, J=8.1 Hz), 8.22 (d, 1H, J=8.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 110.1, 117.8, 124.9, 125.1, 127.5, 128.5, 128.6, 132.3, 132.6, 132.9, 133.2 ppm.

IV.B.5.11. Napthalene-2-carbonitrile

IR (cm^{-1}, KBr): 2226 (-CN), 1594, 1500, 1273, 966, 826, 755, 643. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.58-7.67 (m, 3H), 7.88-7.93 (m, 3H), 8.23 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 109.3, 119.2, 126.3, 127.6, 128, 128.4, 129, 129.1, 132.2, 134.1, 134.6, ppm.

IV.B.6. Supporting spectra

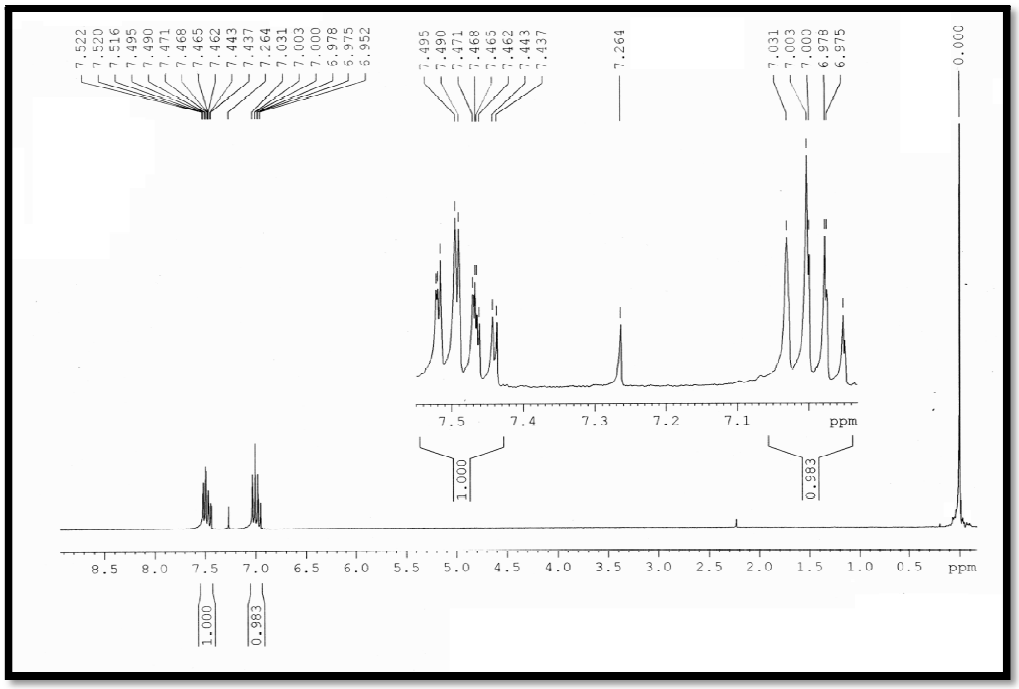


Fig.IV.B.1. [1]H NMR spectrum of 2-Hydroxy benzonitrile

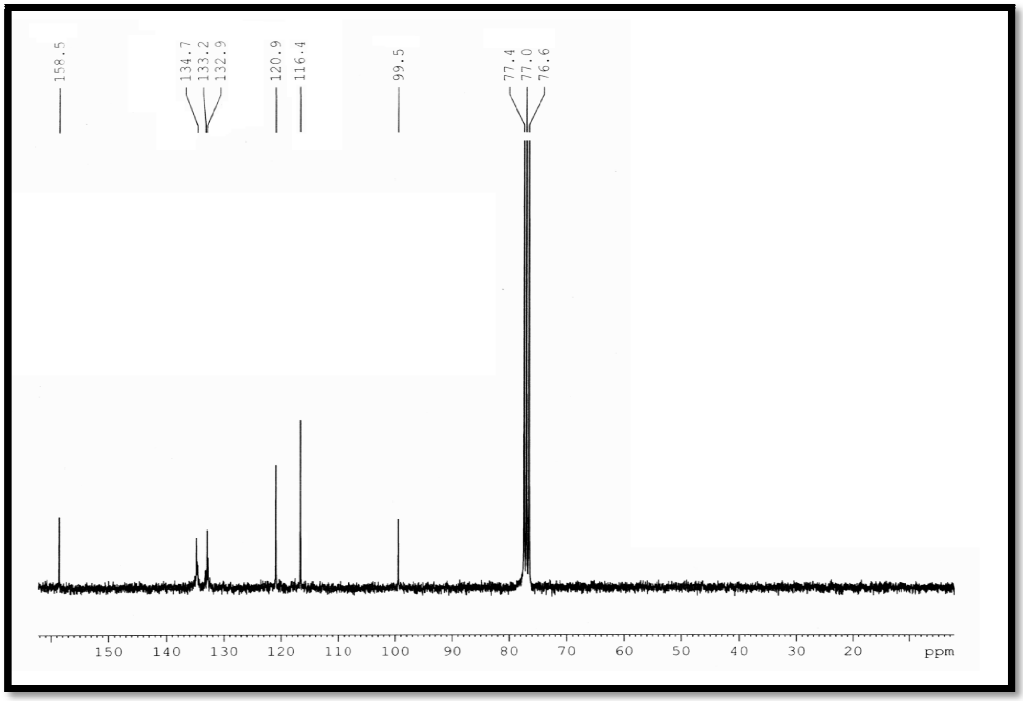


Fig.IV.B.2. [13]C NMR of 2-Hydroxy benzonitrile

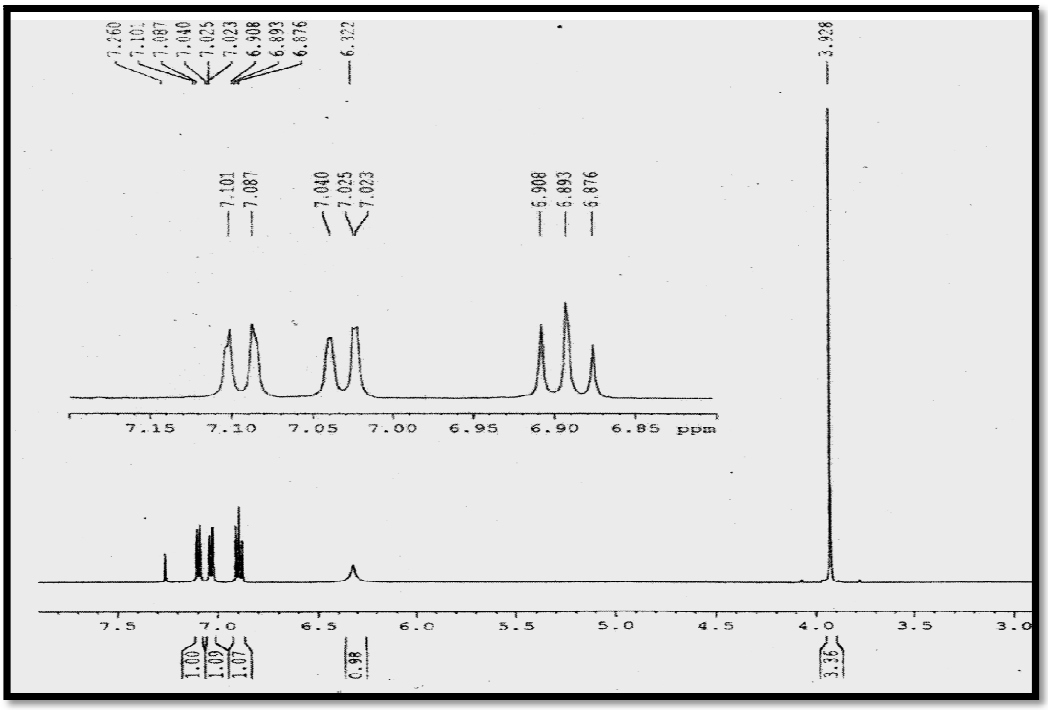


Fig.IV.B.3. ^{1}H NMR of 2-Hydroxy-3-methoxy benzonitrile

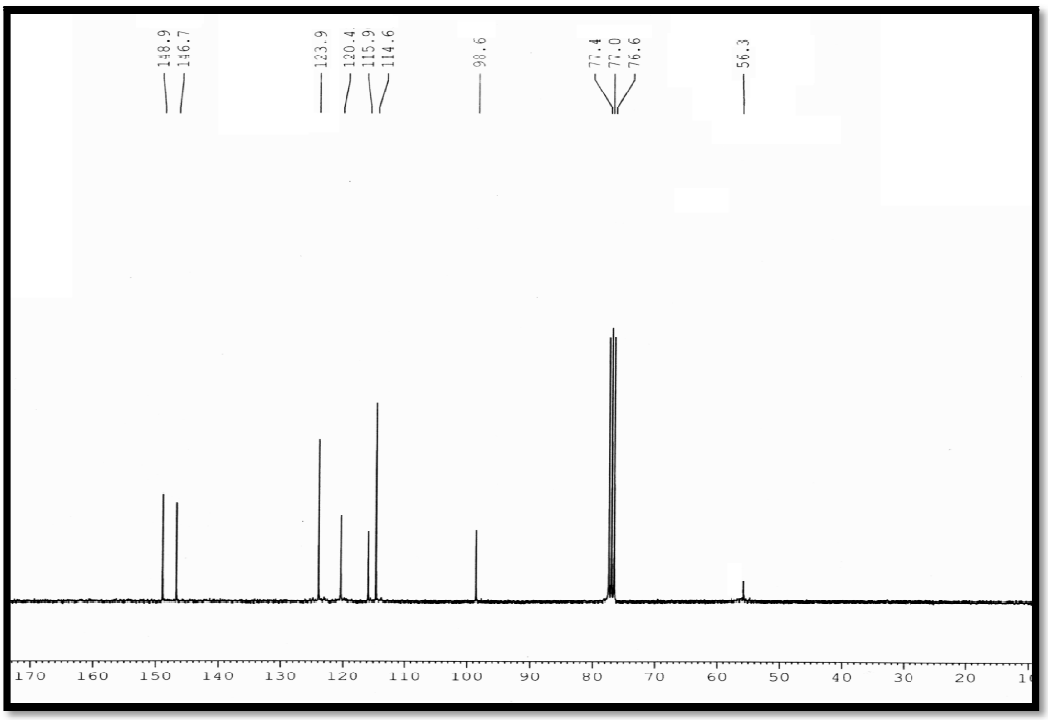


Fig.IV.B.4. ^{13}C NMR of 2-Hydroxy-3-methoxy benzonitrile

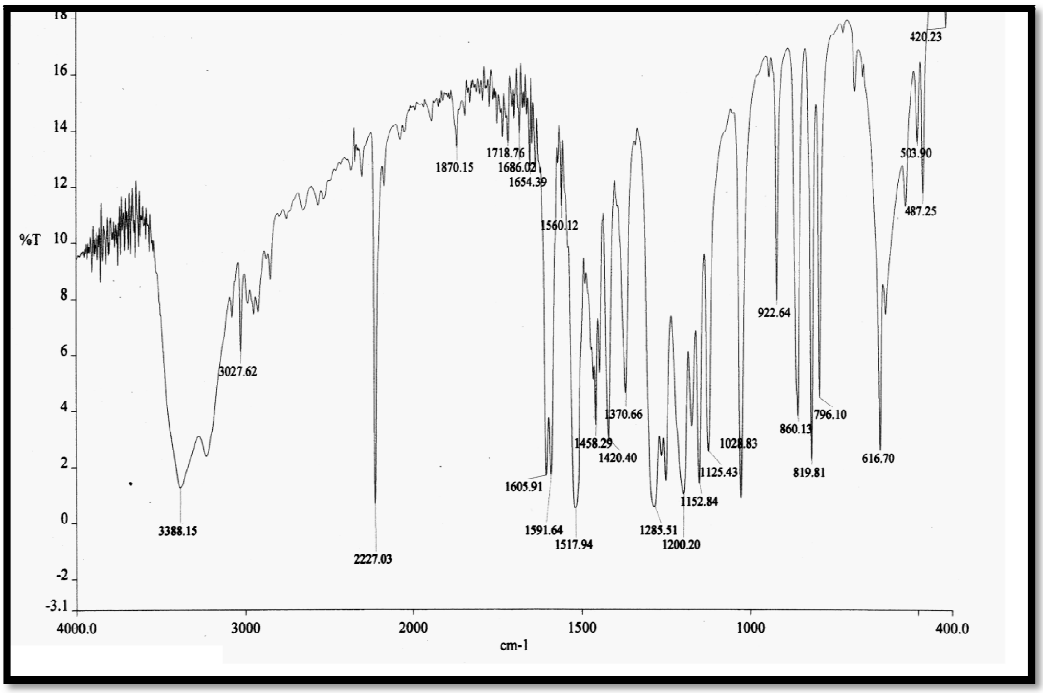


Fig.IV.B.5. FT IR spectrum 3-Methoxy-4-hydroxy benzonitrile

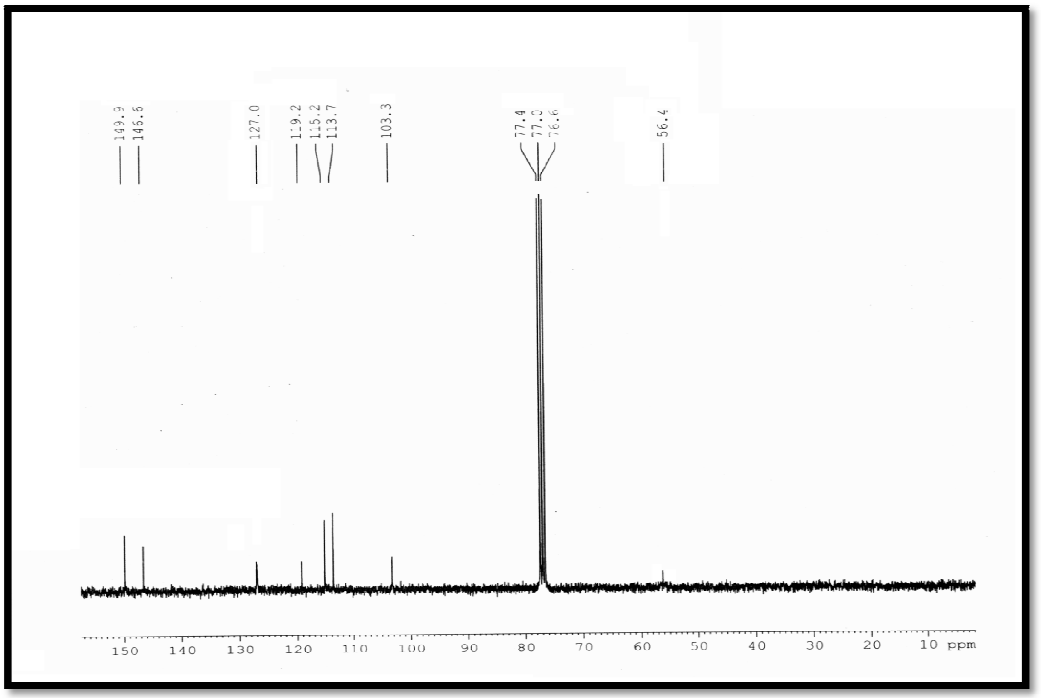


Fig.IV.B.6. ^{13}C NMR spectrum of 3-Methoxy-4-hydroxy benzonitrile

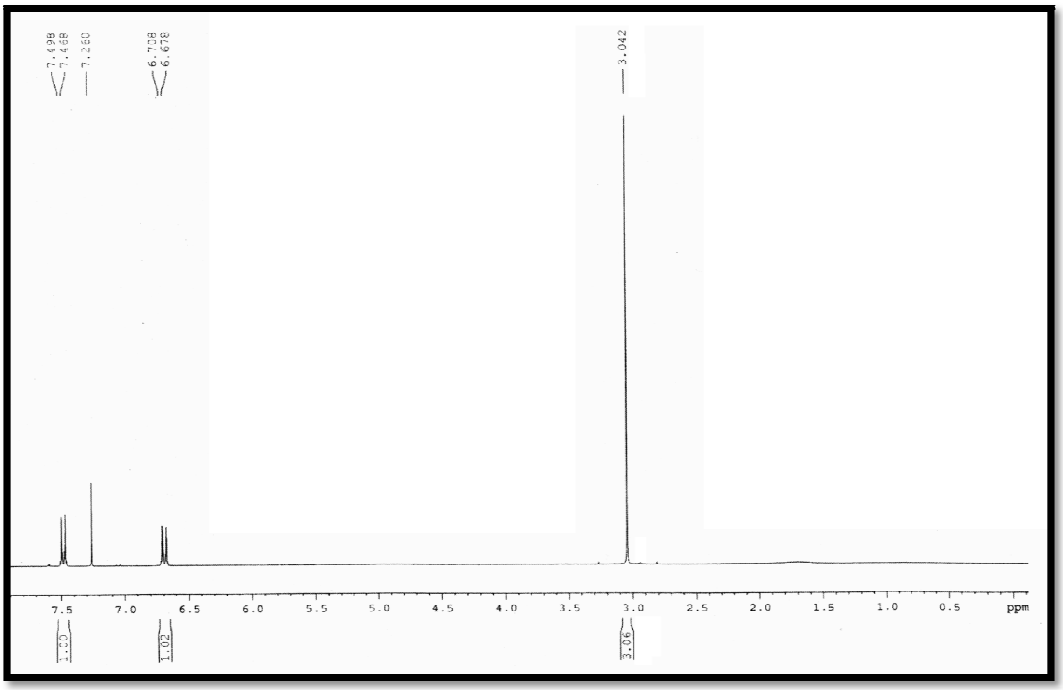


Fig.IV.B.7. ^{1}H NMR of 4-*N,N*-dimethylamino-benzonitrile

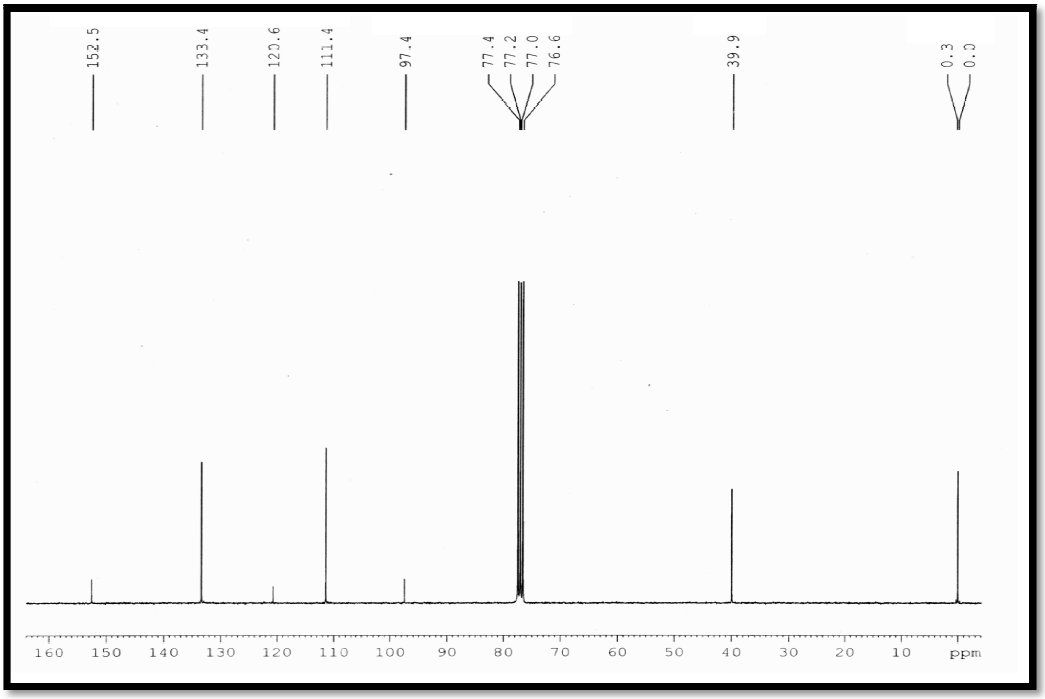


Fig.IV.B.8. ^{13}C NMR of 4-*N,N*-dimethylamino-benzonitrile

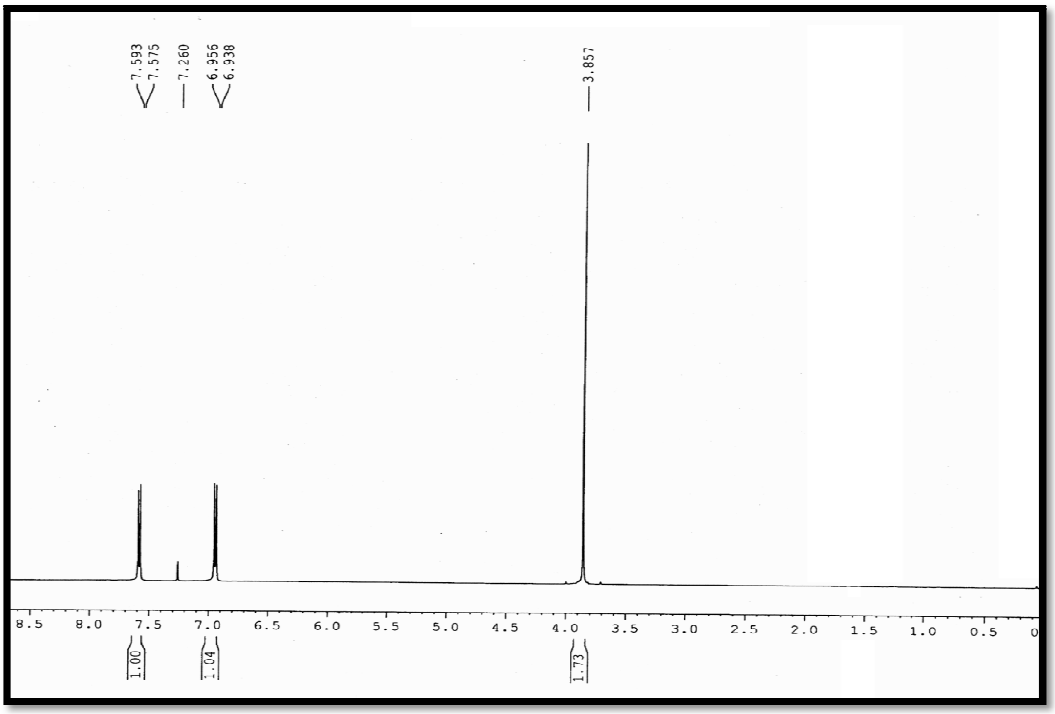


Fig.IV.B.9. ^{1}H NMR of 4-Methoxy benzonitrile

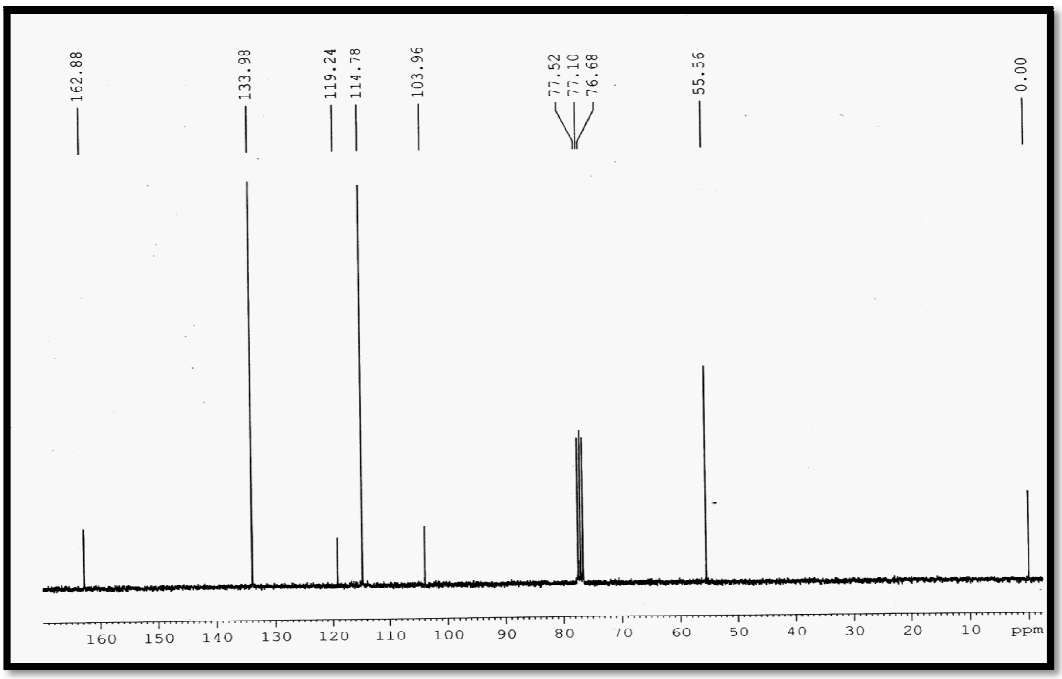


Fig.IV.B.10. ^{13}C NMR of 4-Methoxy benzonitrile

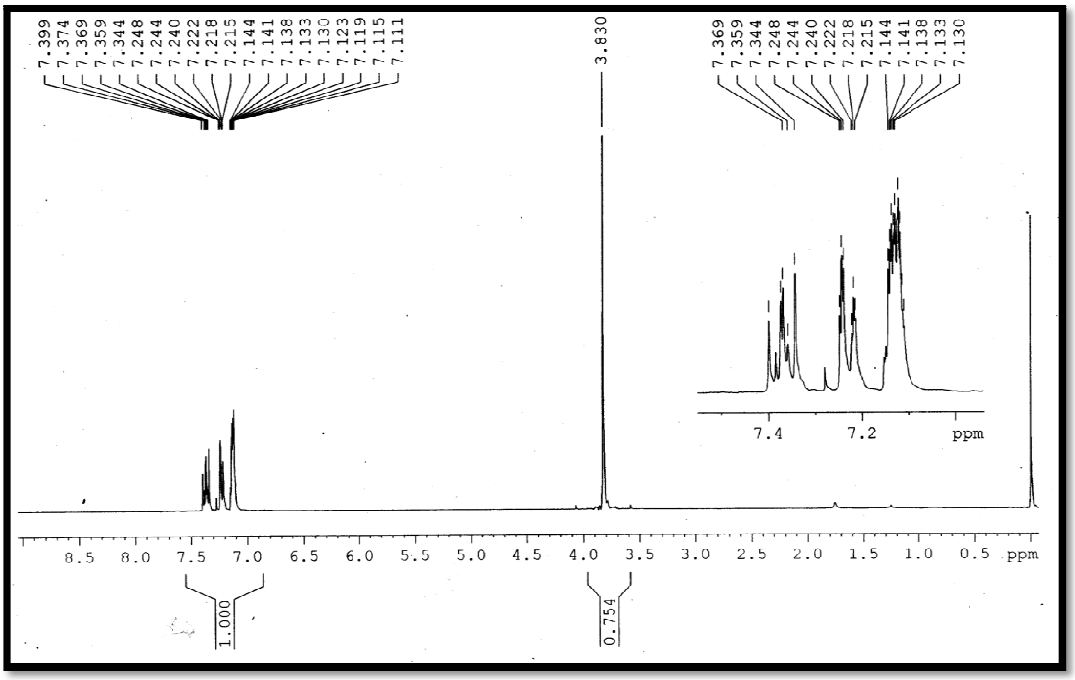


Fig.IV.B.11. ^{1}H NMR of 3-Methoxy benzonitrile

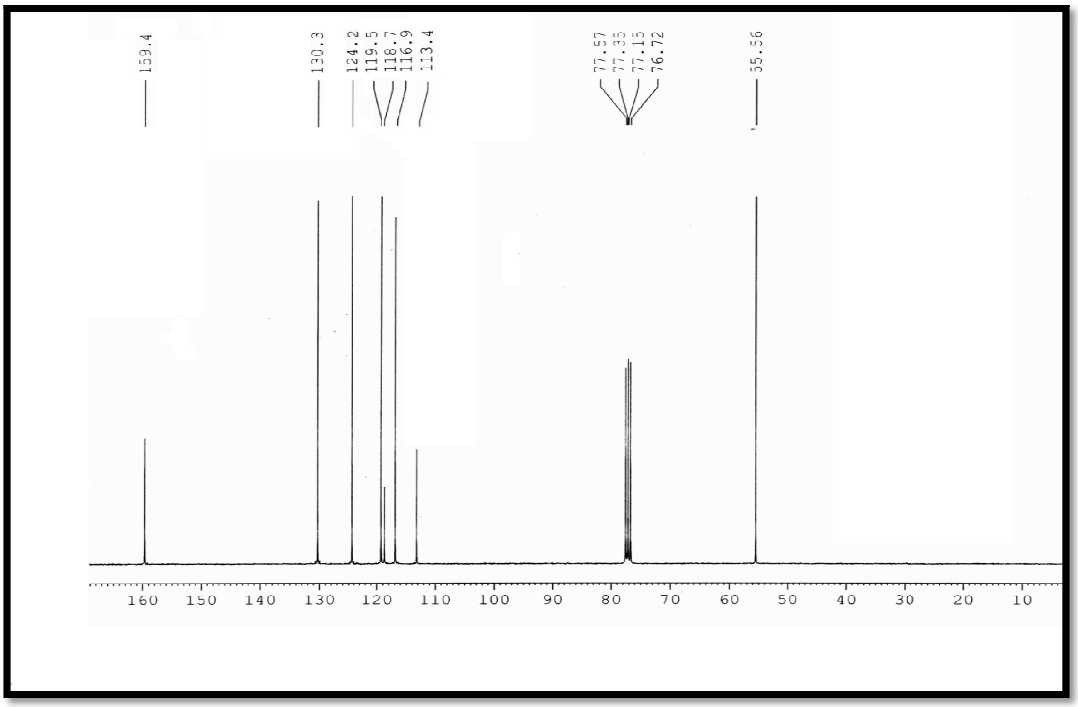


Fig.IV.B.12. ^{13}C NMR spectrum of 3-Methoxy benzonitrile

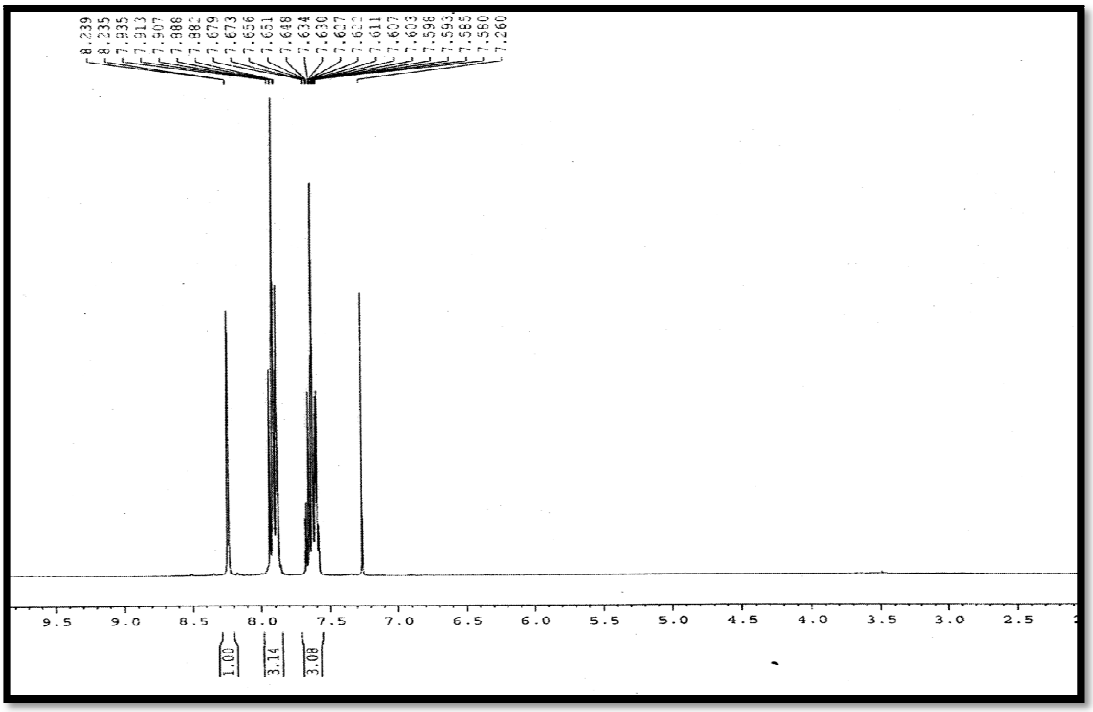


Fig.IV.B.13. ^{1}H NMR spectrum of Napthalene-2-carbonitrile

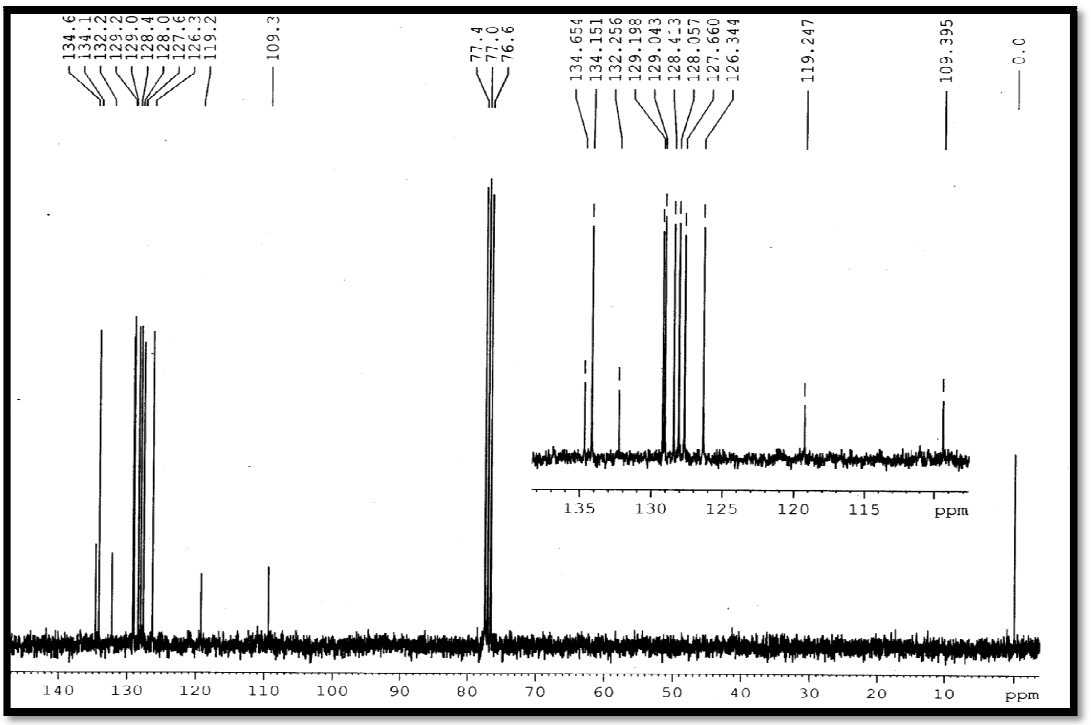


Fig.IV.B.14. ^{13}C NMR spectrum of Napthalene-2-carbonitrile

IV.B.7. References

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CHAPTER-V

$MgCl_2.6H_2O$ catalyzed synthesis of 2-substituted benzimidazoles

CHAPTER-V

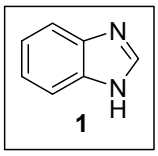
SECTION-A

V.A. A brief review on benzimidazoles, synthesis and its applications

V.A.1. Benzimidazole

Benzimidazole nucleus is a constituent of many bioactive heterocyclic compounds that are of wide interest because of their diverse applications in the field of organic transformation as well as biological applications. Moreover, benzimidazole derivatives are structural isosters of naturally occurring nucleotides, which allows them to interact easily with the biopolymers of the living system. This created interest in researchers who have synthesized variety of benzimidazole derivatives. The incorporation of benzimidazole nucleus, a biologically accepted pharmacophore in medicinal compounds, has made it a versatile heterocyclic moiety possessing wide spectrum of biological activities. The Benzimidazole contains a phenyl ring fused to an imidazole ring. The benzimidazoles are also known as benziminazoles or benzoglyoxalines. They have been also named as derivatives of o-phenylenediamine.

Benzimidazole is a white to slightly beige solid; melting at 172 ^{o}C, boils at 360 ^{o}C, slightly soluble in water, soluble in ethanol. It is a dicyclic compound having imidazole ring (containing two nitrogen atoms at nonadjacent positions) fused to benzene as indicated in the structure of benzimidazole (**1**) (**fig.V.A.1.**).



1

Fig.V.A.1. Benzimidazole

V.A.2. Natural occurance of benzimidazole

The benzimidazole nucleus does not appear to occur very widespread in nature. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitaminB_{12} (**2**) (**fig.V.A.2.**).

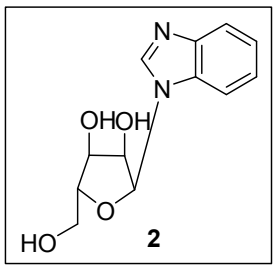


Fig.V.A.2. *N*-ribosyl-dimethylbenzimidazole

V.A.3. Biological profile of benzimidazole

Benzimidazoles are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio. Extensive biochemical and pharmacological studies have confirmed that benzimidazole molecules are effective against various strains of microorganisms. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin-B_{12}. This ring system is present in numerous antiprotozoal,[1] antihelmintics,[2] anti-HIV,[3] anticonvulsant,[4] antiinflammatory,[5] antihepatic[6] and antineoplastic,[7] antiulcer,[8] activities. Resistance to number of antimicrobial agents (β-lactam antibiotics, macrolides, quinolones, and vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly important global problem. In particular, increasing drug resistance among Gram-positive bacteria such as staphylococci, enterococci, and streptococci is a significant health matter. There is real perceived need for the discovery of new compounds endowed with antibacterial activity, possibly acting through mechanisms of action, which are distinct from those of well-known classes of antibacterial agents to which may clinically relevant pathogens are now resistant.[9] Many benzimidazole derivatives are widely used for the treatment of parasitic diseases. Original results of investigations devoted to the antihelminth properties of benzimidazole derivatives, were published within the time period from the middle 1960s to the beginning 1970s.

An original domestic antihelminth drug, approved and allowed for wide clinical use, is medamine synthesized at the Martsinovskii Institute of Medical Parasitology. Mechanisms of the antihelminth activity of these preparations are yet insufficiently studied. It was suggested that the benzimidazole derivatives may selectively and

irreversibly inhibit the absorption of glucose by helminths and produce degenerative changes in the intestinal tract of nematodes and in the absorptive cells of cystodes. At present, more than twenty benzimidazole derivatives are used as antihelminth preparations in the world veterinary and medical practice, including flubendazole (**3**), oxfendazole (**4**)**,** albendazole (**5**), fenbendazole (**6**), triclabendazole (**7**), oxibendazole (**8**), cambendazole (**9**), parbendazole (**10**), nocodazole (**11**), tiabendazole (**112**) (**fig.V.A.3.**).

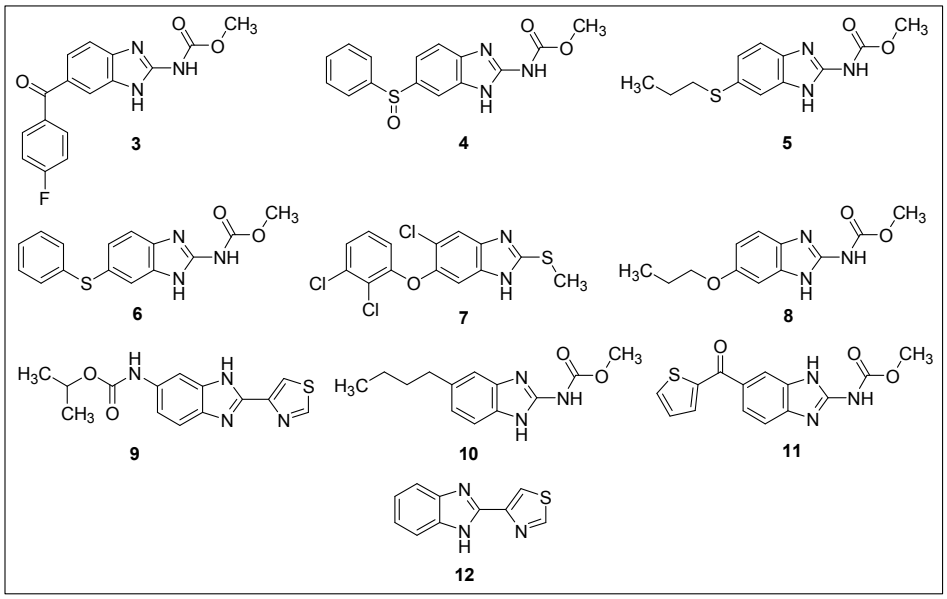


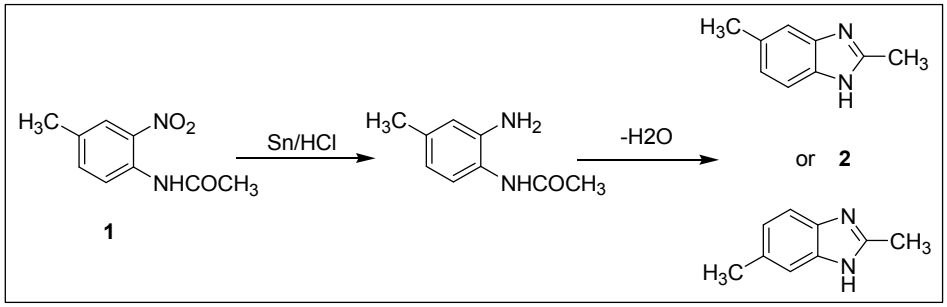
Fig.V.A.3. Examples of benzimidazole drugs

V.A.4. Application of benzimidazole in organic synthesis

Benzimidazoles are one of the versatile compounds having wide application in numerous research areas such as synthesis of tripodal fluorescent receptor bearing benzimidazole motifs as recognition sites in the pods of the receptor which is highly selective fluorescent chemosensor for iodide in aqueous solution,[10] benzimidazole and related ligands for Cu-catalyzed azide-alkyne cycloaddition,[11] hybrid NH_2-benzimidazole ligands for efficient Ru-catalyzed asymmetric hydrogenation of aryl ketones.[12]

V.A.5. Classical method for the synthesis of benzimidazole

Historically, the first benzimidazole was prepared in 1872 by Hoebrecker[13] who obtained 2, 5 or 2, 6-dimethylbenzimidazole (**2**) by the reduction of 2-nitro-4-methylacetanilide (**1**) (**scheme.V.A.1**).



Scheme.V.A.1. Synthesis of benzimidazole from 2-nitro-4-methylacetanilide

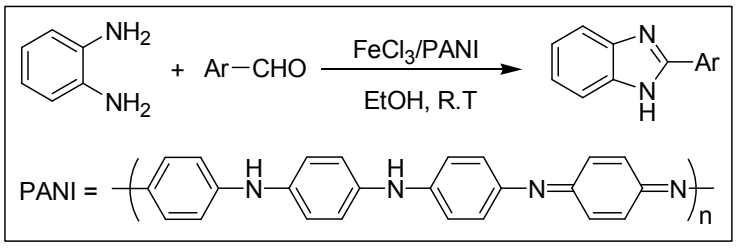
Literature review reveals that, classically, benzimidazoles were synthesized by the condensation of 1, 2-phenylenediamine with carboxylic acid, nitriles, orthoester[14] under very high temperature and strong acidic condition or under microwave irradiation.[15] However, due to the drawbacks of classical method, a numerous new methodologies have been developed for the synthesis of benzimidazole derivatives from the combination of number of functional groups.

V.A.6. Modern methods for the synthesis of benzimidazole derivatives

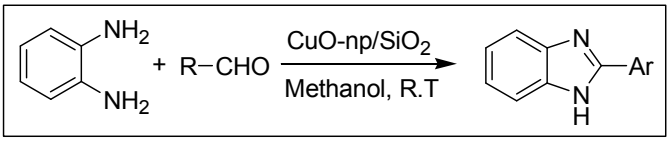
V.A.6.1. Synthesis of benzimidazoles from the combination of 1,2-phenylenediamine and aldehydes under different catalytic conditions

To overcome the limitations of drawbacks of classical methodologies for the preparation of benzimidazole derivatives, the development of modern methodologies was felt necessary. Use of the combination of 1, 2-phenylenediamine and aldehydes is one of the very simple method for the preparation of benzimidazole derivatives. Literature review reveals that wide varieties of catalytic systems have been applied to minimize the drawbacks of reported literature such as lead (IV) oxide (PbO_2) catalyzed synthesis of benzimidazole under solvent free condition,[16] $FeCl_3$-doped polyaniline nanoparticles catalyzed synthesis of 2-substituted benzimidazoles by the reaction of aldehydes with o-phenylenediamine (**scheme.V.A.2.**),[17] iodine mediated synthesis of 2-aryl benzimidazole,[18] synthesis of 2-substituted benzimidazoles using Ti (IV)

isopropoxide and cumene hydroperoxide,[19] selective synthesis of 2-substituted benzimidazole derivatives from the reaction of o- phenylendiamine derivatives and aromatic aldehydes in the presence of NH_4OAc, in absolute ethanol,[20] PEG 400 mediated green synthesis of 2-substituted benzimidazoles under catalyst free and solvent-less condition,[21] the mild synthesis of 2-phenylbenzimidazoles with sodium perborate (SPB) as oxidant,[22] synthesis of 2-substituted potassium (1*H*)-benzimidazoletrifluoroborates by condensation of the corresponding aldehyde with aromatic 1, 2-diamines under oxidative conditions,[23] visible-light driven metal-free green H_2O_2/CAN synthesis of 2-substituted benzimidazole,[24] silica supported reusable nano-copper (II) oxide catalyzed synthesis of 2-substituted benzimidazole (**scheme.V.A.3.**),[25] for the efficient convenient preparation of benzimidazoles under solvent free condition,[26] (bromodimethyl)sulfonium bromide mediated synthesis of benzimidazoles,[27] synthesis of 2-arylbenzimidazole in water,[28] green synthesis of benzimidazoles via an oxidation process with iodine, potassium iodide and potassium carbonate in water,[29] zinc chloride-exchanged K10-montmorillonite (clayzic) is employed as a Lewis acid catalyst in aqueous media at room temperature for the synthesis of various benzimidazoles,[30] animal Bone Meal (ABM) and Lewis acids doped ABMs catalyzed synthesis of 2-substituted benzimidazoles,[31] synthesis of 2-substituted benzimidazoles in organized aqueous media in the presence of a surfactant dodecylbenzenesulfonic acid (DBSA) as catalyst and I_2 as co-catalyst.[32]



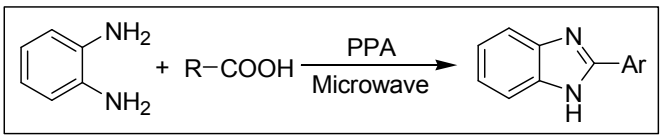
Scheme.V.A.2. $FeCl_3$-doped polyaniline nanoparticles catalyze the synthesis of 2-substituted benzimidazoles



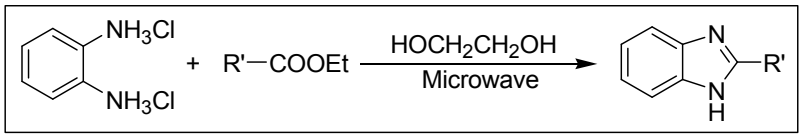
Scheme.V.A.3. Silica supported nano-copper (II) oxide catalyzed synthesis of 2-substituted benzimidazole

V.A.6.2. Synthesis of benzimidazoles from the combination of 1,2-phenylenediamine and carboxylic acids and esters

The condensation of 1, 2-phenylenediamine and organic acids or esters are also a alternative method for the preparation of 2-substituted benzimidazoles. There are various report in literature for the synthesis of substituted benzimidazole by the combination of 1, 2-phenylenediamine and organic acids or esters under diverse catalytic conditions such as polyphosphoric (PPA) catalyzed solvent free synthesis of 2-substituted benzimidazole under microwave irradiation (**scheme.V.A.4.**),[33] N, N-dimethylchlorosulfitemethaniminium chloride promoted synthesis of 2-substituted benzimidazole,[34] zincoxide nanoparticles catalyzed synthesis of benzimidazole derivatives under solvent-free condition,[35] synthesis of 2-alkyl benzimidazoles using natural clay and infrared irradiation under solvent-free condition,[36] propylphosphonic anhydride promoted cyclization of 1, 2-phenylenediamine with carboxylic acids under microwave irradiation.[37] Xiaobi Jing et al. [38] have reported the synthesis of 2-substituted benzimidazole from esters and 1, 2-phenylenediamine hydrochloride under microwave irradiation (**scheme.V.A.5.**) where a variety of 2-substituted benzimidazoles has presented. Limin Wang et al.[39] reported the $Yb(OTf)_3$ catalyzed synthesis of benzimidazoles from the combination of 1, 2-phenylenediamine with ortho-ester.



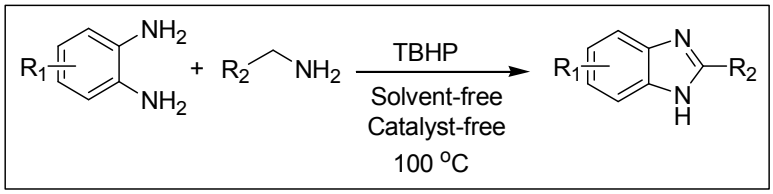
Scheme.V.A.4. PPA catalyzed synthesis of 2-substituted benzimidazole



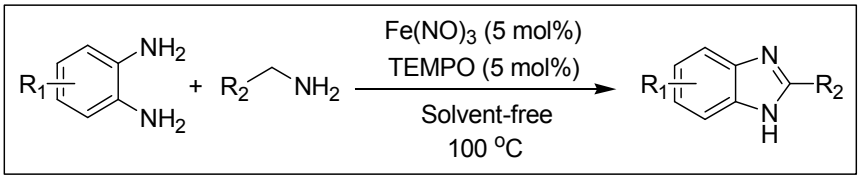
Scheme.V.A.5. Synthesis of benzimidazoles from esters

V.A.6.3. Synthesis of benzimidazoles from the combination of 1, 2-phenylenediamine/2-nitroaniline and amines

The synthesis of benzimidazole moieties by the combination of 1, 2-phenylenediamine with amines instead of aldehydes, acids or esters is one of the attractive alternative approaches. Thanh Binh Nguyen et al.[40] reported the catalyst and solvent free synthesis of 2-substituted benzimidazole from 1, 2-phenylenediamine with amines in the presence of traceless amount of oxidising agent. Later on they again developed a protocol for the synthesis of 2-substitute benzimidazole from 2-nitroaniline and benzyl amines catalyzed by cobalt or iron halide in under solvent free condition.[41] Jiatao Yu et al.[42] reported solvent-free oxidative synthesis of benzimidazoles from arylmethylamines and o-phenylenediamine in the presence of tert-butyl hydroperoxide (TBHP) as the oxidant under catalyst-free condition (**scheme.V.A.6.**). The same group explored the synthetic approach using aromatic primary amines and 1,2-phenylenediamine catalyzed by $Fe(NO_3)_3$/TEMPO under solvent-free conditions in open air at 110 ^oC (**scheme.V.A.7.**).[43]



Scheme.V.A.6. Solvent-free synthesis of benzimidazoles

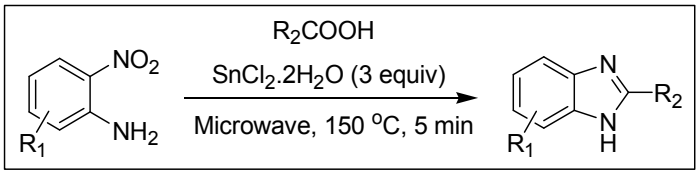


Scheme.V.A.7. $Fe(NO_3)_3$/TEMPO catalyzed synthesis of 2-substituted benzimidazoles

V.A.6.4. Synthesis of benzimidazoles from the combination of 2-nitroaniline and carboxylic acid, alcohol or activated methyl groups

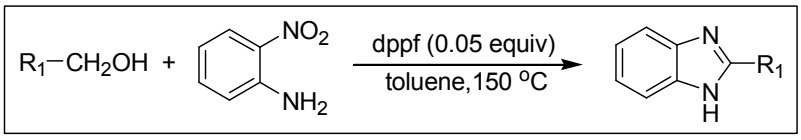
There are few literature reports for the preparation of benzimidazole derivatives from 2-nitroaniline and carboxylic acids, alcohols or activated methyl group. Although the synthesis of these derivatives by this route is difficult, various researchers took a

challenge to develop alternative routes for the synthesis of derivatives of this moiety. David S. VanVliet et al.[44] have reported the preparation of 2-substituted benzimidazoles from 2-nitroaniline and various carboxylice acids in the presence of stannous chloride using microwave irradiation (**scheme.V.A.8.**).



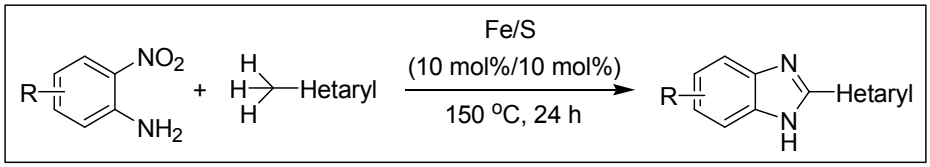
Scheme.V.A.8. Synthesis of 2-substituted benzimidazoles from 2-nitroaniline and carboxylic acids

Haihong Huang et al.[45] have reported iron-catalyzed heterocyclizations from 2-nitroanilines and benzylic alcohols in the presence of dppf [1, 10-bis(diphenylphosphino)-ferrocene] at 150 ^{o}C to form benzimidazoles using hydrogen transfer reaction (**scheme.V.A.9.**).



Scheme.V.A.9. Synthesis of benzimidazoles from 2-nitroanilines and benzylic alcohols

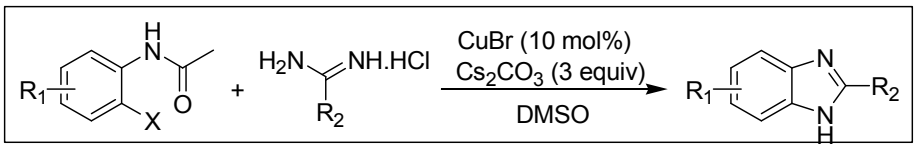
Recently, Thanh Binh Nguyen et al.[46] reported direct coupling of 2-nitroaniline and the methyl group bearing a 2, 4-picolyl or 2-benzimidazolyl substituent providing 2-hetaryl-benzimidazoles. The reaction employs a catalytic amount of iron sulfide generated in situ from the elements under solvent-free conditions (**scheme.V.A.10.**).



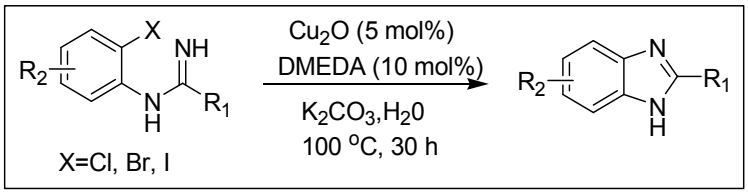
Scheme.V.A.10. Synthesis of substituted benzimidazoles from 2-nitroaniline and methyl hetarenes

V.A.6.5. Synthesis of benzimidazoles by C-X functionalization

Transition metal catalyzed C-X/C-H functionalization for the organic transformations are well known in CuBr catalyzed synthesis of 2-substituted benzimidazoles from *o*-haloacetanilide derivatives and amidine hydrochloride under ligand free conditions (s**cheme.V.A.11.**),[48] CuI/L-Proline catalyzed synthesis of substituted benzimidazoles by coupling of aqueous ammonia with 2-iodoacetanilides,[49] CuI catalyzed synthesis of N-substituted benzimidazoles,[50] Cu_2O in combination with a simple diamine derivative (DMEDA) catalyzed synthesis organic chemistry. There are few numbers of literature report where the transition metals plays excellent catalytic role for the synthesis of substituted benzimidazoles by C-X/C-H bond activation such as, palladium catalyzed synthesis of benzimidazoles using aryl amination chemistry,[47] of substituted benzimidazoles by intramolecular N-arylation in water (**scheme.V.A.12.**),[51] palladium catalyzed synthesis of substituted benzimidazoles from N-(o-halophenyl)-imidoyl chlorides and the corresponding imidates using variety of N-nucleophiles.[52] Recently, Carsten Bolm et al. have reported KOH/DMSO mediated transition metal free synthesis of benzimidazoles by intramolecular N-arylation of amidine,[53] copper or palladium catalyzed the formation of 2-aminobenzimidazoles via intramolecular C-N bond formation between an aryl halide and a guanidine moiety.[54]



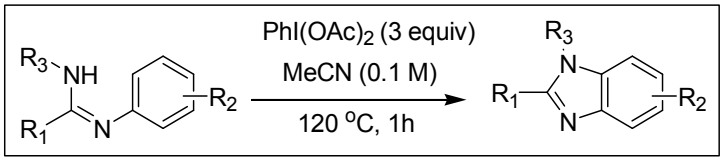
Scheme.V.A.11. CuBr catalyzed synthesis of 2-substituted benzimidazoles



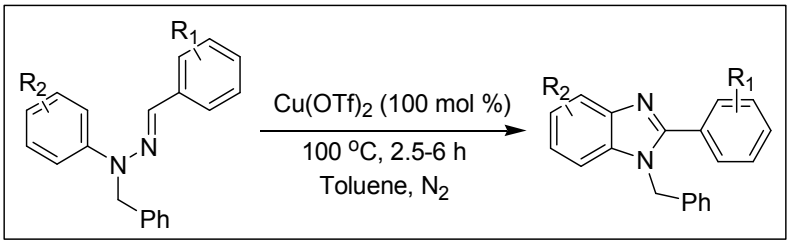
Scheme.V.A.12. Copper catalyzed synthesis of substituted benzimidazoles

V.A.6.6. Synthesis of benzimidazoles by C-H functionalization

Literature review revealed that there are few routes to derivatives of benzimidazoles from C-H bond functionalization. Recently, Ya-Qiu Long et al.[55] reported the TEMPO promoted synthesis of multisubstituted benzimidazoles via metal-free oxidative C-N coupling between the sp^3 C-H and free N−H of readily available N-benzyl/alkyl-1, 2-phenylenediamines. In the same year, the same group have also reported that iodine (III) promoted metal free selective oxidative annulations of aryl amidines for the synthesis of multisubstituted benzimidazoles via C(sp^2)−N bond formation in polar solvent without using any metal salt (**scheme.V.A.13.**).[56] As copper is one of the versatile metals used in various cross-coupling reactions, Tharmalingam Punniyamurthy et al.[57] presented the copper (II)-mediated synthesis of 2-aryl-N-benzylbenzimidazoles from N-benzyl bisarylhydrazones via C-H functionalization (**scheme.V.A.14.**).



Scheme.V.A.13. Synthesis of benzimidazoles via PhI(OAc)2-promoted oxidative annulation in acetonitrile

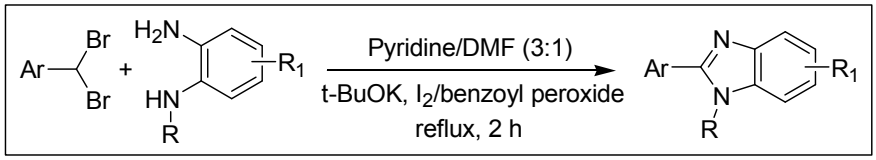


Scheme.V.A.14. Synthesis of substituted benzimidazoles from N-benzyl bisarylhydrazones

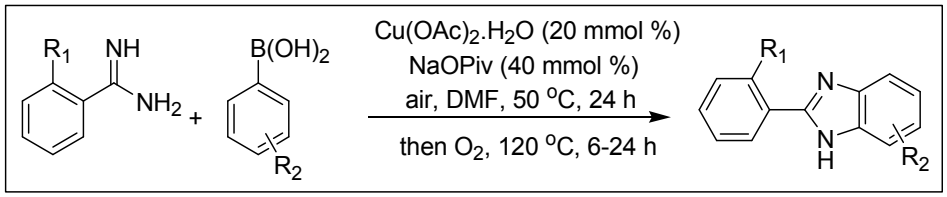
V.A.6.7. Miscellaneous approach for the benzimidazole synthesis

Benzimidazoles derivatives can also be synthesized other methods by taking varieties of starting materials. Wang Shen et al.[58] have reported the preparation of substituted benzimidazoles from 1, 1-dibromoethenes and o-diaminobenzenes in mildly basic conditions. Kanchugarakoppal S. Rangappa et al.[59] have used gem-dibromomethylarenes as condensing partner with o-diaminoarenes to form substituted

benzimidazole derivatives (**scheme.V.A.15.**). The combination of alcohols and 1,2-phenylenediamine is also a good alternative approach for the synthesis of substituted benzimidazole derivatives. Kanchugarakoppal S. Rangappa et al.[60] have recently reported propylphosphonic anhydride mediated one-pot synthesis of benzimidazole derivatives from wide variety of alcohols. The synthesis from amidines and aryl boronic acid via N-arylation and C-H bond activation is also successfully carried out by Jieping Zhu et al.[61] (**scheme.V.A.16.**). In this reaction, Jieping Zhu et al. have used catalytic amount of copper acetate and sodium pivalate under aerobic condition at 50 ^{o}C followed by intramolecular direct C-H bond functionalization but under oxygen at 120 ^{o}C to afford benzimidazole derivatives.

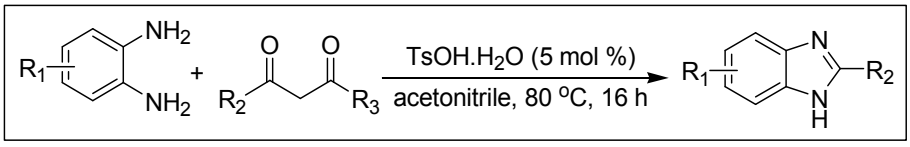


Scheme.V.A.15. Synthesis of benzimidazoles from gem-dibromomethylarene



Scheme.V.A.16. Copper catalyzed synthesis of benzimidazoles

Xiangge Zhou et al.[62] have reported Cu_2O catalyzed synthesis of benzimidazole derivatives from amidine hydrochlorides and o-haloanilines. Benzimidazole derivatives can also be prepared by the condensation between 1, 2-diaminoarenes and 1, 3-diketo derivatives. Ming Bao et al.[63] have reported the Brønsted acid catalyzed synthesis of benzimidazole derivatives by cyclization of 1, 2-diaminoarenes with β-diketones without using oxidant, metal salts and radiation (**scheme.V.A.17.**).



Scheme.V.A.17. Brønsted acid catalyzed synthesis of benzimidazole

V.A.7. Conclusion

Because of enormous applications of benzimidazoles towards pharmaceuticals and organic synthesis, people have devoted their time to develop new methodologies to overcome the shortcomings of classical method for the synthesis of these derivatives. The literature review revealed that wide varieties of catalytic systems have been applied for the synthesis of benzimidazole derivatives. But many of the reported methodologies are not simple, easy and cost-efficient. Based on the literature reports, author felt necessary to develop an easy, cost-efficient and simple method for the preparation of these derivatives which meet the present day demand under the aspect of sustainable development.

V.A.8. References

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CHAPTER-V

SECTION-B

$MgCl_2.6H_2O$ catalyzed synthesis of 2-substituted benzimidazoles

V.B. Present Investigation

V.B.1. Background of the present investigation

Benzimidazole is an important substructure found in wide range of bioactive compounds [1] and in pharmaceuticals.[2] They are the key structural intermediate in the synthesis of variety of bioactive compounds. These moieties serves as important intermediates in numerous organic reaction[3] and used as important ligands for transition metals in various organic transformations.[4] The broad utility of these moieties has prompted significant efforts toward their synthesis. Classically, benzimidazoles were synthesized by the condensation of 1, 2-phenylenediamine with carboxylic acid, nitriles, orthoester[5] under very high temperature and strong acidic condition or under microwave irradiation.[6] In the last decades, use of various catalytic system has been established for the synthesis of benzimidazole derivatives from 1, 2-phenylenediamine and aldehydes such as $PhI(OAc)_2$,[7] DDQ,[8] heteropoly acids,[9] Zn-proline,[10] MnO_2,[11] H_2O_2/HCl,[12] H_2O_2/CAN,[13] oxone,[14] $NaHSO_3$,[15] $Na_2S_2O_5$,[16] sulfamic acid,[17] $FeCl_3.6H_2O$,[18] $KHSO_4$,[19] $ZrCl_4$,[20] $In(OTf)_3$,[21] $Yb(OTf)_3$,[22] $Sc(OTf)_3$,[23] $Cu(OTf)_2$,[24] p-TSA,[25] polymer-supported hypervalent iodine,[26] cobalt(II) chloride hexahydrate,[27] $Sm(OTf)_3$,[28] thiamine hydrochloride,[29] $FeCl_3$-doped polyaniline nanoparticles,[30] mixture of Ti(IV) isopropoxide and cumene hydroperoxide,[31] animal bone meal,[32] nano ceria,[33] cobalt (II) hydroxide and oxide,[34] Zn^{2+}-K10-clay,[35] laccase,[36] 4-methoxy TEMPO,[37] CuO nano-particles supported silica,[38] sodium perborate.[39] The direct synthesis of these heterocycles by C-X bond activation[40] and from 2-nitro aniline in combination with benzyl amine/benzyl alcohol by redox reaction[41] are also well known in the literature. However, most of these reported protocols suffer from one or more drawbacks such as drastic reaction conditions, long reaction time, poor yield, side product formation, use of expensive catalyst, use of toxic reagent and hazardous solvent, use of excessive oxidant, work-up difficulties, which makes them undesirable under the aspect of green chemistry, sustainable development and industrial applications. In view of ample applications of benzimidazole as a potent bioactive material as well as precursor for

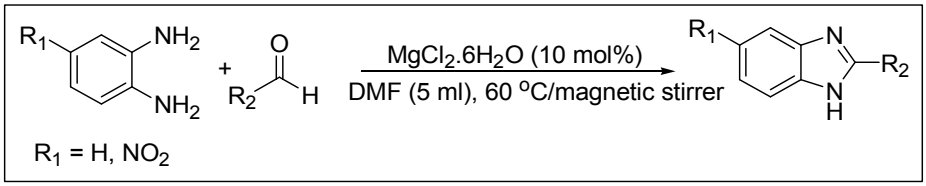
constructing the new molecules and designing the metal-carbene catalyst[42] for various organic transformations, there is still demand of mild, easy and environmentally benign reaction protocol for the its synthesis.

It is well documented[43] that, magnesium is a versatile metal for organometallic chemistry and various catalytic organic syntheses, and is highly abundant, inexpensive, less toxic and environmentally benign metal. It plays key role in fundamental biological processes, in catalysis and designing various organometallic reagents. The literature survey reveals that the catalytic activity of magnesium salt are prominent in the synthesis of various organic compounds such as 3, 4-dihydropyrimidine-2-(1H)-ones,[44] 4-chloro-3-hydroxy-2-pyrone,[45] 3-carboxy-4-oxo-1,8-napthyridines,[46] acylation of diethyl fluoromethylphosphonate.[47] Because of its versatility, significant catalytic activity, low toxicity, high functional group tolerance, and inexpensiveness, magnesium salt has gain special attention in modern organic synthesis. However, to the best of our knowledge, the well known catalytic competence of magnesium chloride hexahydrate has never been attempted so far for the synthesis of 2-substituted benzimidazole. With these backgrounds of magnesium salt, and in view of development of mild, easy, straight forward and cheap and reaction protocol, we have chosen magnesium chloride hexahydrate as preeminent reagent for the synthesis of 2-substituted benzimidazole.

V.B.2. Results and discussion

In continuation of our efforts to develop a mild and highly efficient protocol for the organic synthesis and transformations,[48] we herein report $MgCl_2.6H_2O$ catalyzed a mild and facile synthesis of 2-substituted benzimidazoles from the reaction of 1, 2-phenylenediamine/4-nitro-1, 2-phenylenediamine with aryl, heteroaryl aldehydes in the presence of 10 mol % $MgCl_2.6H_2O$ in DMF (5 ml) (**scheme.V.B.1.**). For our model reaction, we have chosen 3-methoxy benzaldehyde and 1,2-phenylenediamine as our model starting materials for desired transformation. The model reaction comprising of 1, 2-phenylenediamine (1 mmol) and 3-methoxy benzaldehyde (1 mmol) in DMF at room temperature furnished only 36 % 2-substituted benzimidazole after 15 h (**entry 1, table.V.B.1.**). The same reaction when carried out in the presence of 20 mol% of $MgCl_2.6H_2O$ enhanced the yield of the product upto 61% (**entry 2, table.V.B.1.**). And finally we could optimize the reaction temperature to obtain the product 97 % in 1.5 h at 60 ^oC (**entry 5, table.V.B.1.**). However, under identical condition but in the absence of

the catalyst only 58% product was isolated after 7 h (**entry 6, table.V.B.1.**). The optimization of catalyst loading indicated that (**entry 3, table.V.B.2.**) only 10 mol% of $MgCl_2.6H_2O$ and 5 mL of solvent (DMF) per mmole of the reactant ratio is sufficient for the conversion upto 96% yield of the desired product. We again screened the effect of catalyst from room temperature to 70 ^oC. The optimum temperature for the reaction was found to be 60 ^oC (**table.V.B.3.**).



Scheme.V.B.1. Synthesis of 2-substituted benzimidazoles

Table.V.B.1

[a]Optimization of temperature

Entry	Temperature (^oC)	Time (h)	Catalyst (mol %)	Yield (%)[b]
1	r.t	15	nil	36
2	r.t	5	20	61
3	40	5	20	72
4	50	3	20	86
5	60	1.5	20	97
6	60	7	nil	58

[a]Optimization of temperature: Reaction of 1,2-phenylenediamine (1 mmol), 3-methoxy benzaldehyde (1 mmol) in presence as well as in absence of catalyst in 5 mL DMF.

[b]Isolated yield.

Table.V.B.2

[c]Optimization of catalyst at 60 ^{o}C

Entry	Catalyst (mol %)	Time (h)	Yield (%)[b]
1	20	1.5	97
2	15	1.5	96
3	10	1.5	96
4	8	1.5	92
5	5	1.5	87

[c]The reaction of of 1, 2-phenylenediamine (1 mmol), 3-methoxy benzaldehyde (1 mmol) amount of catalyst was slowly reduced from 20 mol%.

Table.V.B.3

[d]Optimization of temperature in the presence of 10 mol % catalyst

Entry	Temperature (^{o}C)	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	r.t	10	1.5	58
2	40	-	1.5	66
3	50	-	1.5	84
4	60	-	1.5	96
5	70	-	1.5	96

[d]The reaction of of 1, 2-phenylenediamine (1 mmol), 3-methoxy benzaldehyde (1 mmol). The optimum temperature was found to be 60 ^{o}C.

The reactions were carried out in nine different solvents under optimized temperature and amount of catalyst, to examine the effect of solvent (**table.V.B.4.**). Solvent optimization clearly suggested that DMF as the best solvent for the desired transformation (**table.V.B.4**). For the generalization of our scheme, aldehydes (**1-16**) were treated with 1, 2-phenylenediamine under optimized condition to obtain (86-96 %) of the desired products. It was evident from (**table.V.B.5**) that the yield of the product does not vary much with the functionally substituted aldehydes. No product from aliphatic aldehydes were found, the poor reactivity of aliphatic carbonyl compound may be because of possible enolization of aliphatic carbonyls.

Table.V.B.4

[e]Screening of solvent

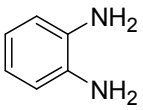
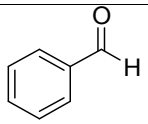
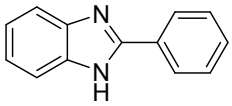
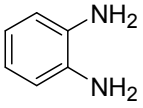
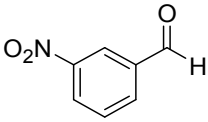
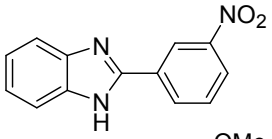
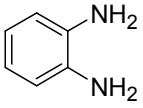
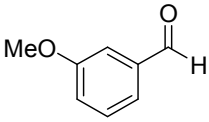
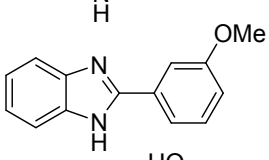
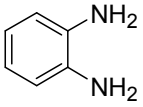
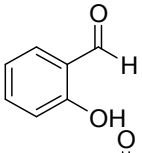
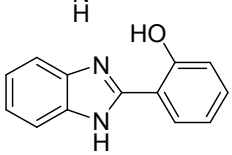
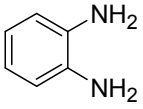
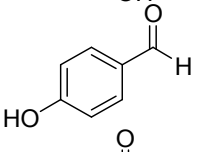
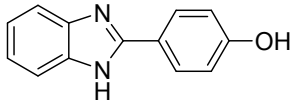
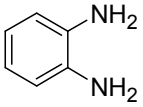
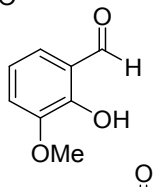
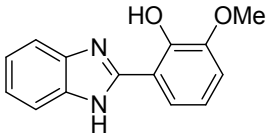
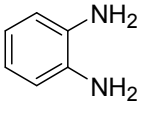
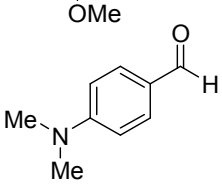
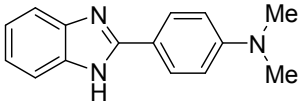
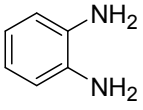
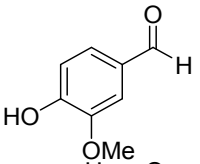
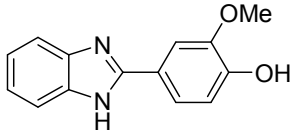
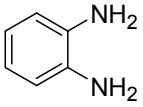
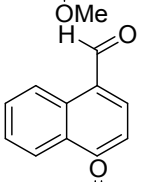
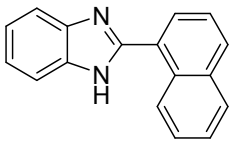
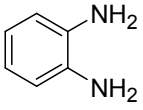
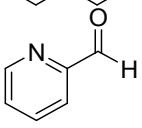
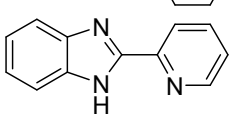
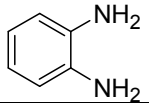
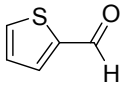
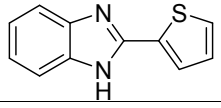
Entry	Solvent	Time (h)	Yield %[b]
1	H_2O	8	54
2	CH_3OH	6	62
3	CH_3CH_2OH	6	74
4	$CHCl_3$	4	48
5	THF	5	72
6	1,4-Dioxan	2.5	93
7	DMF	1.5	96
8	CH_3CN	4	79
9	DMSO	3	81

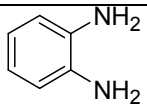
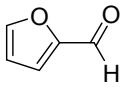
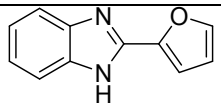
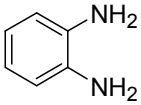
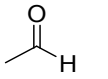
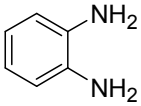
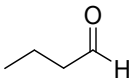
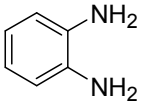
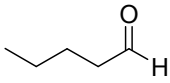
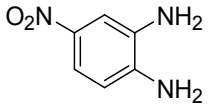
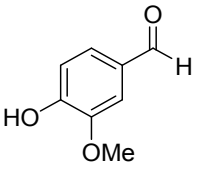
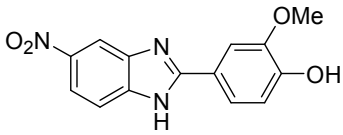
[e]Solvent screening: the eaction of 1, 2-phenylenediamine (1 mmol), 3-methoxy benzaldehyde (1 mmol) and 10 mol% catalyst at 60 ^oC.

As 4-nitro-1, 2-phenylenediamine has deactivated amine function which is not good substrate for the condensation reaction. The efficiency of the protocol were also tested by synthesizing the 2-substituted benzimidazoles from 4-nitro-1, 2-phenylenediamine (**entry 16, table.V.B.5**). The excellent yield of the product indicates that the protocol is equally efficient towards the deactivated amino functions. Comparatively long reaction time is required for this reaction, it may be because of deactivated amino function of 4-nitro-1, 2-phenylenediamine.

Table.V.B.5

$MgCl_2.6H_2O$ catalyzed synthesis of 2-substituted benzimidazole

Entry	Amine	Aldehydes	Time (min)	Product	Yield (%)[b]
1			100		93
2			70		96
3			90		96
4			110		89
5			120		88
6			130		90
7			150		91
8			140		86
9			90		93
10			110		90
11			80		86

12			100		88
13			100	-	NR[c]
14			100	-	NR
15			100	-	NR
16			240		88

[c]NR = no reaction.

V.B.3. Experimental

V.B.3.1.Chemicals

All the chemicals which were used for the present investigation are listed in the **table.V.B.6.** The details of the chemicals regarding their source and purity are summarised in **table.V.B.6.**

Table.V.B.6.

Chemicals used for the present investigation

Entry	Chemical	Source	Purity (%)
1	Benzaldehyde	Sigma-Aldrich	98
2	3-Nitrobenzaldehyde	LOBA Chemie	98
3	3-Methoxybenzaldehyde	Chemical Book	97
4	2-Hydroxybenzaldehyde	S.D Fine	99
5	4-Hydroxybenzaldehyde	S.D Fine	98
6	2-Hydroxy-3-methoxybenzaldehyde	ACROS	99
7	N,N-dimethyl-4-aminobenzaldehyde	Sigma-Aldrich	99
8	3-Methoxy-4-hydroxybenzaldehyde	S.D Fine	99
9	1-Napthaldehyde	Sigma-Aldrich	95

10	Pyridine-2-carboxaldehyde	Sigma-Aldrich	99
11	2-Thiophene-carboxaldehyde	Sigma-Aldrich	98
12	Furfural	Sigma-Aldrich	99
13	1, 2-phenylenediamine	Fisher Scientific	98
14	4-Nitro-1, 2-phenylenediamine	Sigma-Aldrich	98
15	Magnesium chloride hexahydrate	Sigma-Aldrich	99
16	Sodium sulphate anhydrous	SRL	99.5
17	DMF	Merck	98
18	Petroleum ether	T.B	98
19	Ethyl acetate	T.B	99
20	Silica gel 60-120 mesh for column	SRL	-
21	Silica gel for TLC	SRL	-
22	Potassium bromide for IR	Merck	99
23	$CDCl_3$ for NMR	ACROS	99.8
24	DMSO-d_6 for NMR	ACROS	99.8

V.B.3.2. Reaction procedure and purification

To a mixture of 1, 2-phenylenediamine (1 mmol) and aldehyde (1 mmol) in DMF (5 ml) under open atmosphere, 10 mol% of the catalyst was added. The resulting mixture was stirred at 60 ^{o}C for appropriate time (table 5). The completion of reaction was monitored by TLC; the reaction mixture was cooled to room temperature and poured into 20 ml water. The product was extracted with ethyl acetate, washed with water and dried over Na_2SO_4. It was purified by column chromatography using neutral alumina and petroleum ether-ethylacetate as the eluent.

V.B.3.3. Spectroscopic measurements

Melting points were determined by open capillary method and hence are uncorrected. IR spectra were recorded on KBr disks in the range 4000-400 on Shimadzu FT-IR 8300 Spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on 300 MHz Bruker Avance FT NMR Spectrometer using TMS as internal standard.

V.B.4. Conclusion

In conclusion, we have developed a new protocol for facile synthesis of 2-substituted benzimidazoles from combining 1,2-phenylenediamine (1mmol) with aryl and heteroaryl aldehydes (1mmol) in the presence of $MgCl_2.6H_2O$ (10 mol%) in DMF (5 ml) at 60 ^oC. Excellent yield, cost efficient, high functional group tolerance, environmentally benign, and simple work-up process are the added advantages of this protocol.

V.B.5. Spectroscopic data

V.B.5.1. 2-Phenyl-1*H*-benzimidazole

Mp 292-295 ^oC. Found: C, 80.37 %; H, 5.16 %; N, 14.4 %. Calculated for $C_{13}H_{10}N_2$ (194.2): C, 80.39 %; H, 5.19 %; N, 14.42 %. IR (cm^{-1}, KBr): 3058, 1560, 1252, 694. ^1H NMR (300 MHz, DMSO-d_6): δ, 7.19-7.22 (m, 2H), 7.46-7.61 (m, 5H), 8.18-8.21 (m, 2H), 12.89 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 122.6, 126.9, 129.4, 130.3, 130.6, 151.7 ppm.

V.B.5.2. 2-(3-Nitro phenyl)-1*H*-benzimidazole

Mp 254-256 ^oC. Found: C, 65.26 %; H, 3.78 %; N, 17.57 %; O, 13.32 %. Calculated for $C_{13}H_9N_3O_2$ (239.23): C, 65.27 %; H, 3.79, %; N, 17.56 %, O, 13.38 %. IR (cm^{-1}, KBr): 3370, 3090, 1655, 1518, 810. ^1H NMR (300 MHz, DMSO-d_6): δ, 7.22-7.29 (m, 2H), 7.57(d, 1H, J=7.5Hz), 7.71 (d, 1H, J=7.5Hz), 7.80-7.86 (m, 1H), 8.29-8.32 (m, 1H), 8.60 (d, 1H, J=7.8Hz), 8.99-9.01 (m, 1H) 13.27 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 112.1, 119.7, 121.2, 122.6, 123.7, 124.6, 131.1, 132.1, 132.9, 135.5, 144.0, 148.8, 149.5 ppm.

V.B.5.3. 2-(3-Methoxy phenyl)-1*H*-benzimidazole

Mp 196-198^oC. Found: C, 74.99 %; H, 5.37 %; N, 12.48 %; O, 7.12 %. Calculated for $C_{14}H_{12}N_2O$ (224.2): C, 74.98 %; H, 5.39 %; N, 12.49 %, O, 7.13 %. IR (cm^{-1}, KBr): 3067, 1655, 830. ^1H NMR (300 MHz, DMSO-d_6): δ, 3.86 (s, 3H), 7.03-7.07 (m, 1H), 7.18-7.23 (m, 2H), 7.43-7.48 (m, 1H), 7.60 (s, 2H), 7.74-7.77 (m, 2H), 12.9 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 55.7, 111.8, 111.8, 116.3, 119.2, 122.5, 130.5, 131.9, 151.5, 160.1 ppm.

V.B.5.4. 2-(2-Hydroxy phenyl)-1*H*-benzimidazole

Mp 276-278 ^{o}C. Found: C, 74.26 %; H, 4.74 %; N, 13.34 %; O, 7.63 %. Calculated for $C_{13}H_{10}N_2O$ (210.23): C, 74.27 %; H, 4.79 %; N, 13.33 %, O, 7.61 %. IR (cm^{-1}, KBr): 3327, 3047, 1590, 799. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 6.99-7.06 (m, 2H), 7.28-7.41(m, 3H), 7.66 (br band, 2H), 8.06 (d, 1H, J=7.8Hz), 13.18 (s, 2H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 111.9, 113.0, 117.6, 118.4, 119.5, 122.9, 123.6, 126.6, 132.2, 152.1, 158.4 ppm.

V.B.5.5. 2-(4-Hydroxy phenyl)-1*H*-benzimidazole

Mp 253–255 ^{o}C. Found: C, 74.24 %; H, 4.78 %; N, 13.35 %; O, 7.62 %. Calculated for $C_{13}H_{10}N_2O$ (210.23): C, 74.27 %; H, 4.79 %; N, 13.33 %, O, 7.61 %. IR (cm^{-1}, KBr): 3360, 3570, 1565. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 6.7-6.75 (m, 2H), 6.91-6.97 (m, 2H), 7.33 (s, 2H), 7.79-7.85 (m, 2H), 9.94 (s, 1H, -OH), 12.47 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 111.6, 121.5, 122.1, 128.6, 152.2, 159.6 ppm.

V.B.5.6. 2-(2-Hydroxy, 3-methoxy phenyl)-1*H*-benzimidazole

Found: C, 69.96 %; H, 5.13 %; N, 11.63 %; O, 13.33 %. Calculated for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99 %; H, 5.03 %; N, 11.66 %, O, 13.32 %. IR (cm^{-1}, KBr): 3336, 3067, 1593, 1422, 743. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 3.82 (s, 3H), 6.92-6.97 (m, 1H), 7.06-7.09 (m, 1H), 7.25-7.31 (m, 2H), 7.61-7.64 (m, 3H), 13.25 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 56.1, 112.9, 114.2, 117.9, 119.2, 123.3, 148.7, 149.0, 152.3 ppm.

V.B.5.7. 2-(4-*N,N*-dimethyl phenyl)-1*H*-benzimidazole

Mp 295-298 ^{o}C. Found: C, 75.89 %; H, 6.36 %; N, 17.72 %. Calculated for $C_{15}H_{15}N_3$ (237.3): C, 75.92 %; H, 6.37 %; N, 17.71 %. IR (cm^{-1}, KBr): 3047, 1593, 1493, 765. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 2.99 (s, 6H), 6.81-6.85 (m, 2H), 7.1-7.16 (m, 2H), 7.48-7.53(m, 2H), 7.97-8.02 (m, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 40.2, 112.3, 117.7, 121.8, 128, 151.7, 152.7 ppm.

V.B.5.8. 2-(4-Hydroxy, 3-methoxy phenyl)-1*H*-benzimidazole

Found: C, 69.98 %; H, 5.07 %; N, 11.68 %; O, 13.34 %. Calculated for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99 %; H, 5.03 %; N, 11.66 %, O, 13.32 %. IR (cm^{-1}, KBr): 3339, 3068, 1595, 741. ^1H NMR (300 MHz, DMSO-d_6): δ, 3.94 (s, 3H), 6.99-7.02 (m, 2H), 7.21-7.23 (m, 2H), 7.61-7.72 (m, 3H), 7.84 (s, 1H), 10.11 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 56.1, 110.8, 114.8, 116.1, 120.1, 121.7, 122.2, 148.3, 148.9, 152.3 ppm.

V.B.5.9. 2- (Napthyl-1yl)-1*H*-benzimidazole

Mp 196-198 ^oC. Found: C, 83.56 %; H, 4.94 %; N, 11.46 %. Calculated for $C_{17}H_{12}N_2$ (244.29): C, 83.58 %; H, 4.95 %; N, 11.47 %. IR (cm^{-1}, KBr): 3057, 1560, 774.4. ^1H NMR (300 MHz, DMSO-d_6): δ, 7.19-7.23 (m, 2H), 7.52-7.66 (m, 4H), 7.61(d, 1H, J= 6.6 Hz), 7.96-8.05 (m, 3H), 9.06 (d, 1H, J=8.1 Hz), 12.89 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 111.8, 119.5, 122.0, 123.1, 125.7, 126.8, 127.5, 127.9, 128.3, 128.8, 130.6, 130.9, 134.0, 134.9, 144.3, 151.8 ppm.

V.B.5.10. 2-(Pyridin- 2yl)-1*H*-benzimidazole

Mp 216-219 ^oC. Found: C, 73.84 %; H, 4.66 %; N, 21.51 %. Calculated for $C_{12}H_9N_3$ (195.22): C, 73.83 %; H, 4.65 %; N, 21.52 %. IR (cm^{-1}, KBr): 3057, 1593, 744. ^1H NMR (300 MHz, DMSO-d_6): δ, 7.21-7.23 (m, 2H), 7.49-7.53 (m, 3H), 7.96-8.02 (m, 1H), 8.30-8.34 (m, 1H), 8.72-8.74 (m, 1H), 13.09 (s, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ, 121.8, 125.2, 138.0, 149.0, 149.8, 151.2 ppm.

V.B.5.11. 2-(Thiophene-2yl)-1*H*-benzimidazole

Mp >290^oC. Found: C, 65.96 %; H, 4.02 %; N, 13.97 %; S, 16.01 %. Calculated for $C_{11}H_8N_2S$ (200.26): C, 65.97 %; H, 4.03 %; N, 13.99 %; S, 16.01 %. IR (cm^{-1}, KBr): 3051, 1571, 1423, 743. ^1H NMR (300 MHz, DMSO-d_6): δ, 7.2-7.24 (m, 3H), 7.57 (br band, 2H), 7.71 (d, 1H, J=0.9 Hz), 7.73 (d, 1H, J=0.9 Hz), 12.94 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 111.6, 119.0, 122.2, 122.9, 127.1, 128.7, 129.1, 134.1, 147.4 ppm.

V.B.5.12. 2-(Furan-2-yl)-1*H*- benzimidazole

Found: C, 71.71 %; H, 4.36 %; N, 15.22 %; O, 8.67 %. Calculated for $C_{11}H_8N_2O$ (184.19): C, 71.73 %; H, 4.38 %; N, 15.21 %; O, 8.69 %. IR (cm^{-1}, KBr): 3058, 1655, 1525, 1417, 979, 738. ^1H NMR (300 MHz, DMSO-d_6): δ, 6.71-6.76 (m, 1H), 7.18-7.22 (m, 3H), 7.54-7.57 (s, 2H), 7.93-7.97 (m, 1H), 12.94 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 110.9, 112.7, 122.7, 144.1, 145, 146 ppm.

V.B.5.13. 2-(4-Hydroxy, 3-methoxy phenyl)-5-nitro-1*H*-benzimidazole

Found: C, 58.94 %; H, 3.87 %; N, 14.72 %; O, 22.41 %. Calculated for $C_{14}H_{11}N_3O_4$ (285.25): C, 71.73 %; H, 4.38 %; N, 15.21 %; O, 8.69 %. IR (cm^{-1}, KBr): 3338, 3069, 1587. ^1H NMR (300 MHz, dmso-d_6): δ, 3.85 (s, 3H), 7.13-7.25 (m, 2H), 7.67-7.76 (m, 1H), 8.14-8.48 (m, 4H), 13.48 (s, 1H, -NH) ppm. ^{13}C NMR (75 MHz, dmso-d_6): δ, 56.2, 111.3, 116.3, 118.1, 120.6, 121, 142.8, 148.4, 150, 156.8 ppm.

V.B.6. Supporting spectra

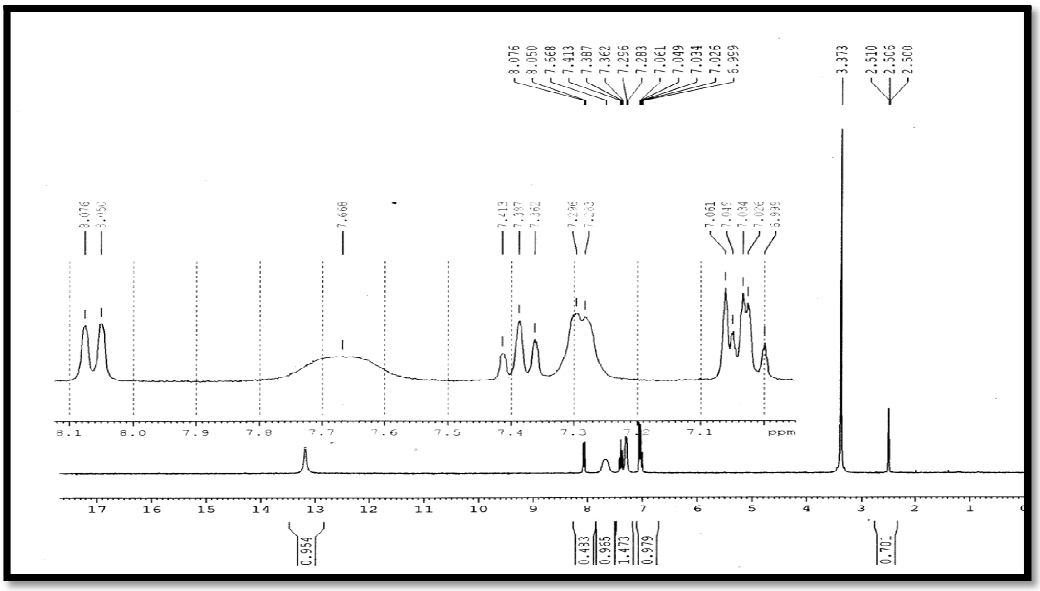


Fig.V.B.1. ^{1}H NMR spectrum of 2-(2-Hydroxy phenyl)-1*H*-benzimidazole

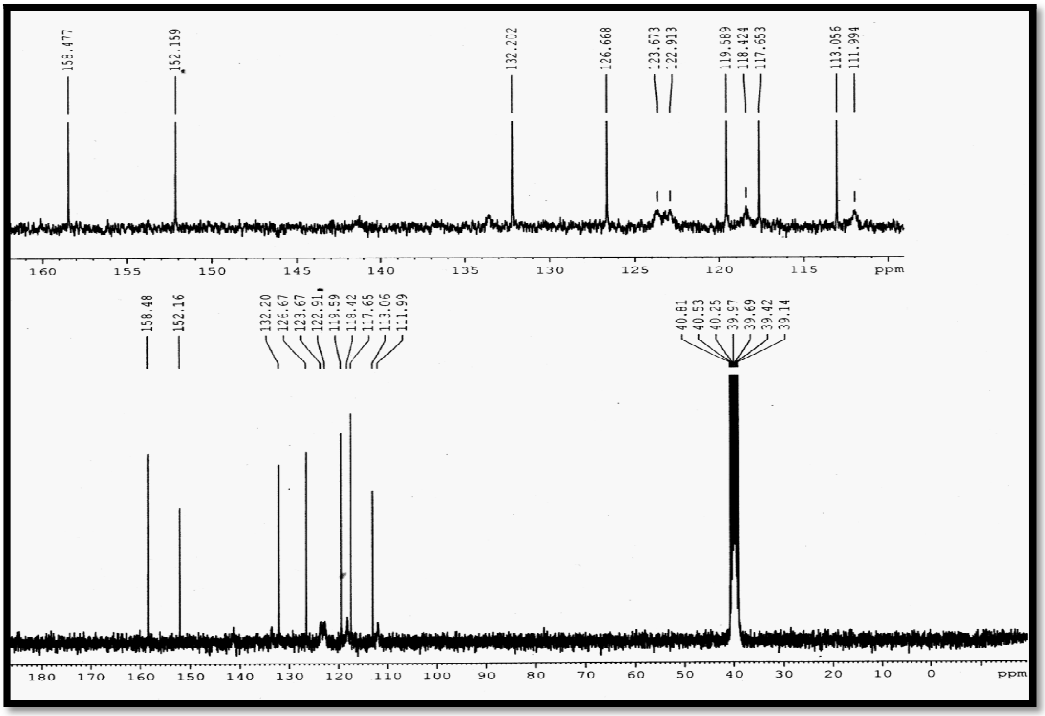


Fig.V.B.2. ^{13}C NMR spectrum of 2-(2-Hydroxy phenyl)-1*H*-benzimidazole

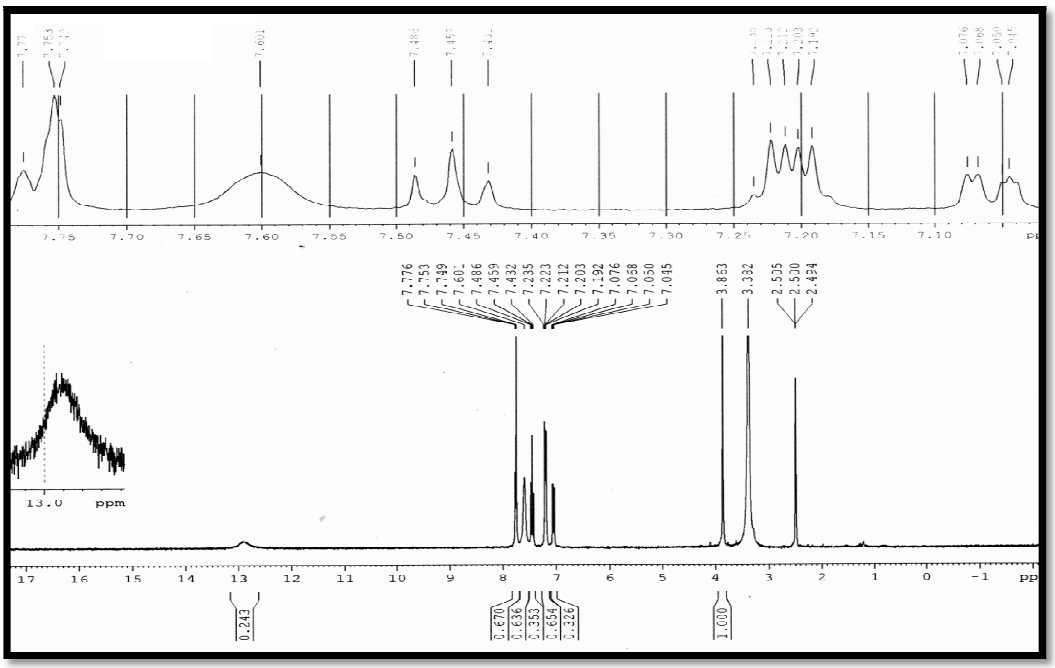


Fig.V.B.3.[1]H NMR spectrum of 2-(3-Methoxy phenyl)-1*H*-benzimidazole

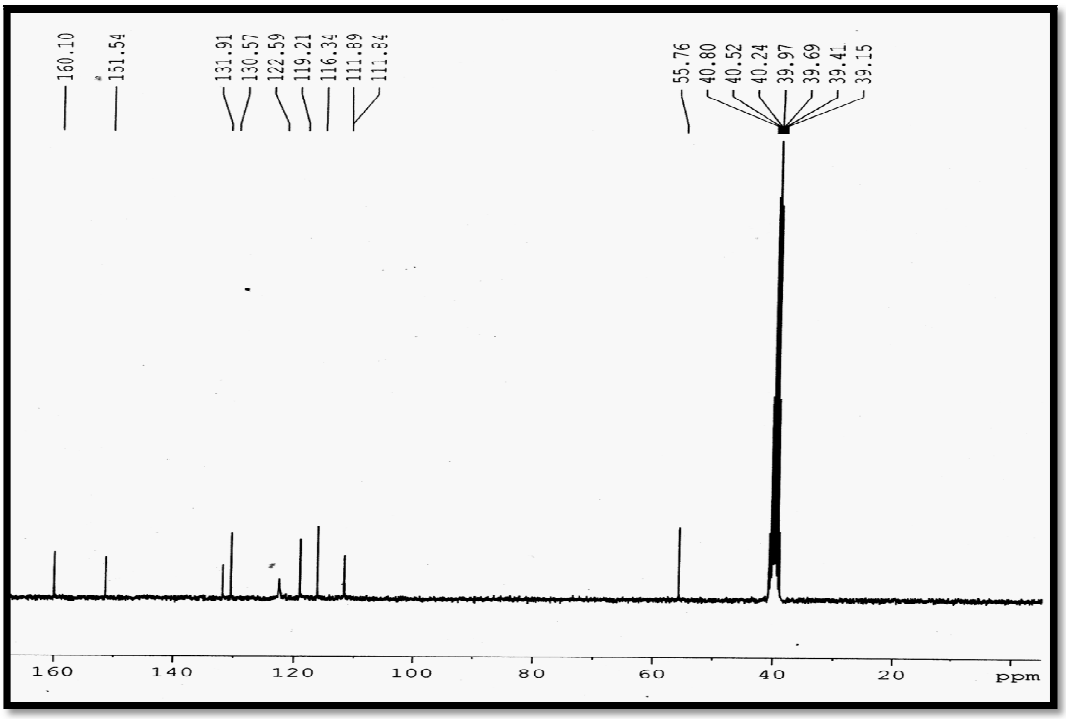


Fig.V.B.4.[13]C NMR spectrum of 2-(3-Methoxy phenyl)-1*H*-benzimidazole

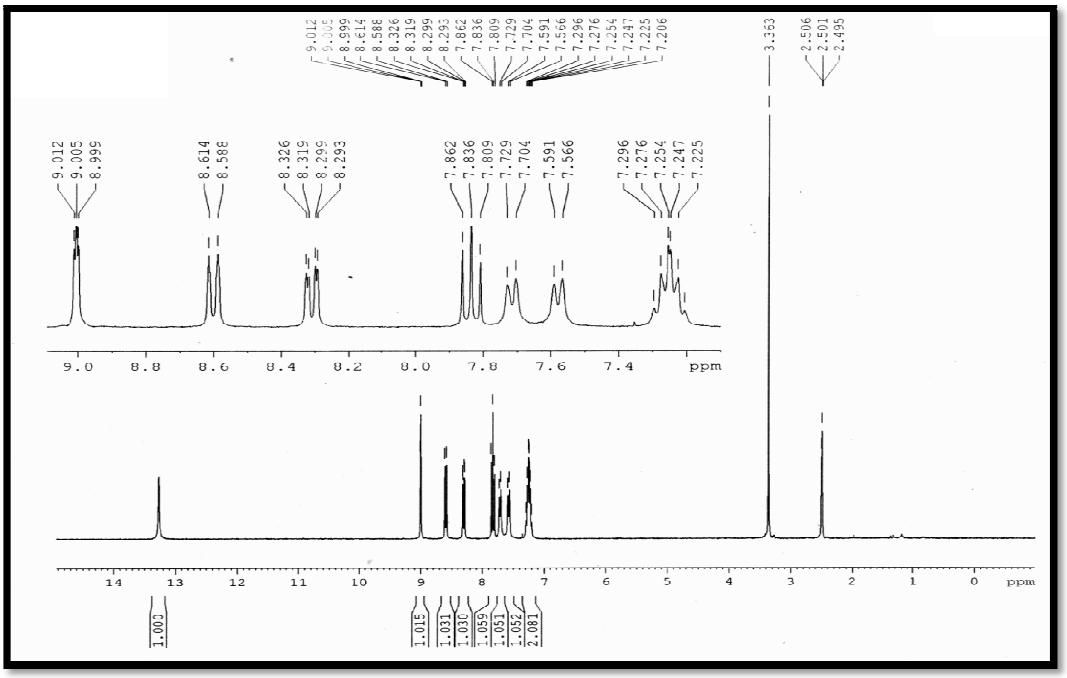


Fig.V.B.5.[1]H NMR spectrum of 2-(3-Nitro phenyl)-1*H*-benzimidazole

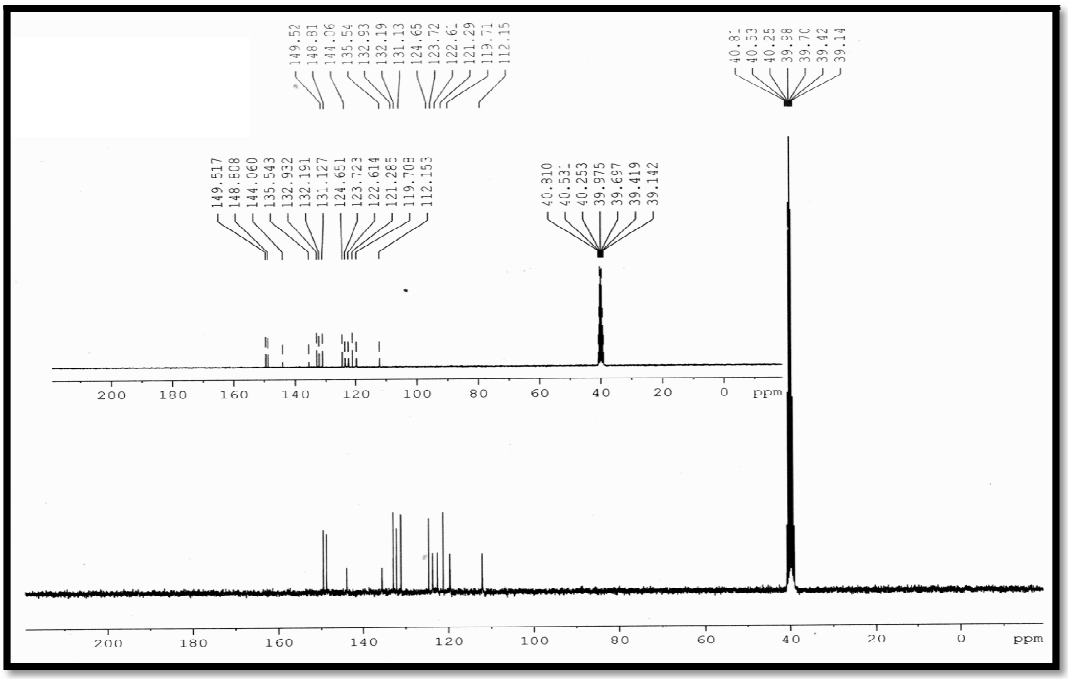


Fig.V.B.6.[13]C NMR spectrum of 2-(3-Nitro phenyl)-1*H*-benzimidazole

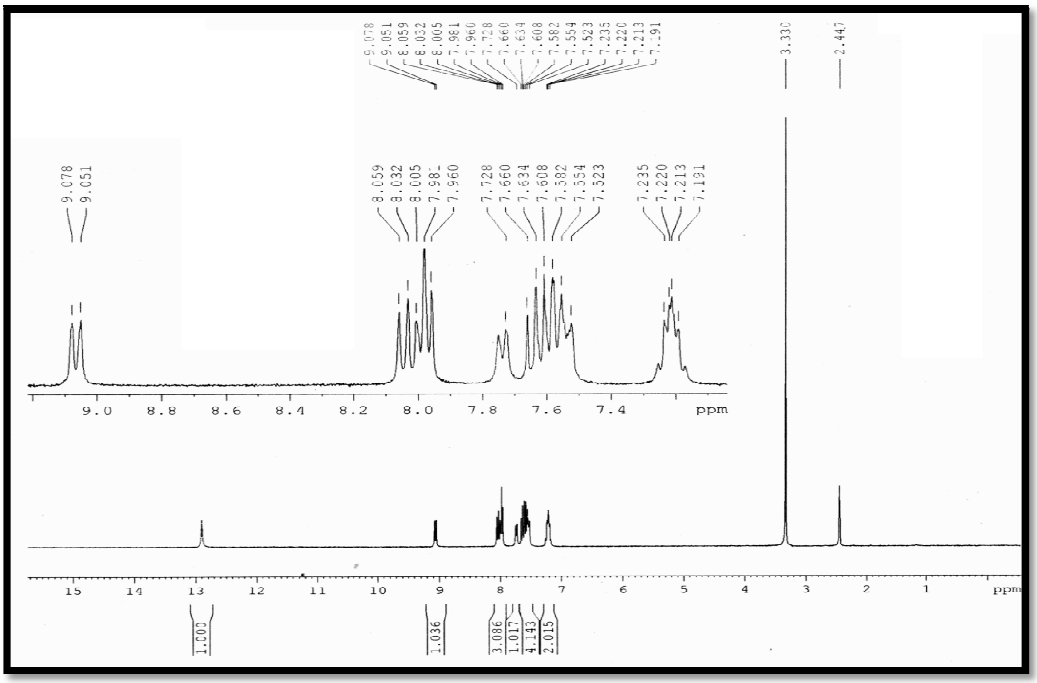


Fig.V.B.7.[1]H NMR spectrum of 2- (Napthyl-1yl)-1*H*-benzimidazole

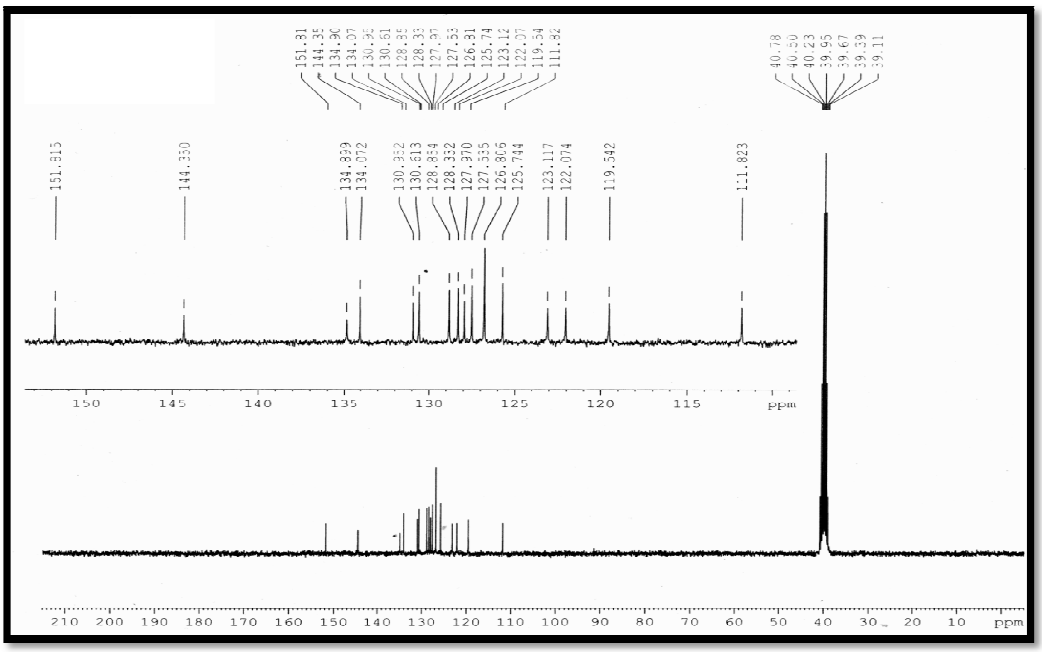


Fig.V.B.8.[13]C NMR spectrum of 2- (Napthyl-1yl)-1H-benzimidazole

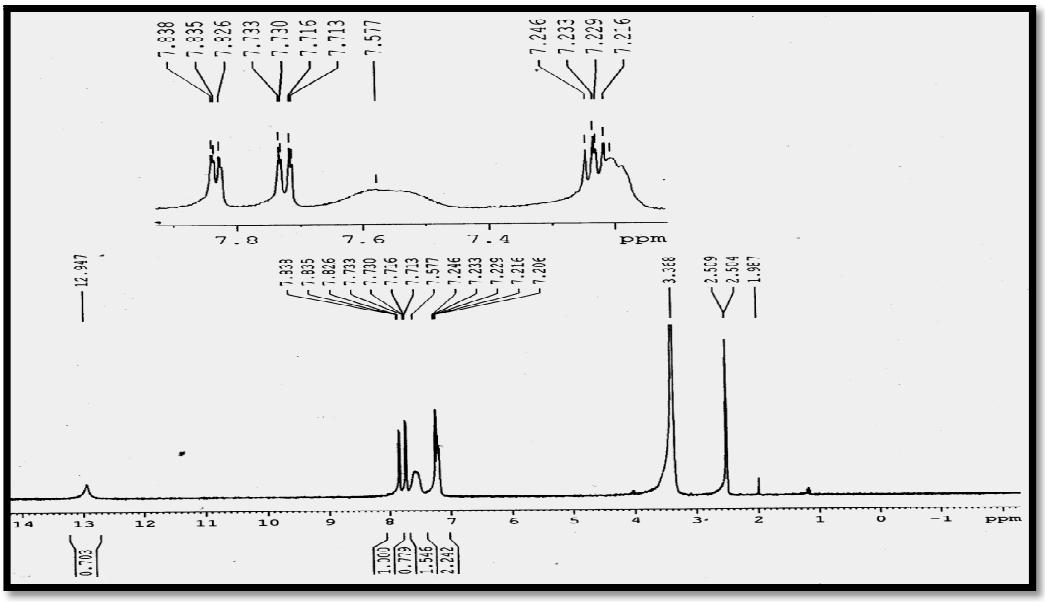


Fig.V.B.9.[1]H NMR spectrum of 2-(Thiophene-2yl)-1H-benzimidazole

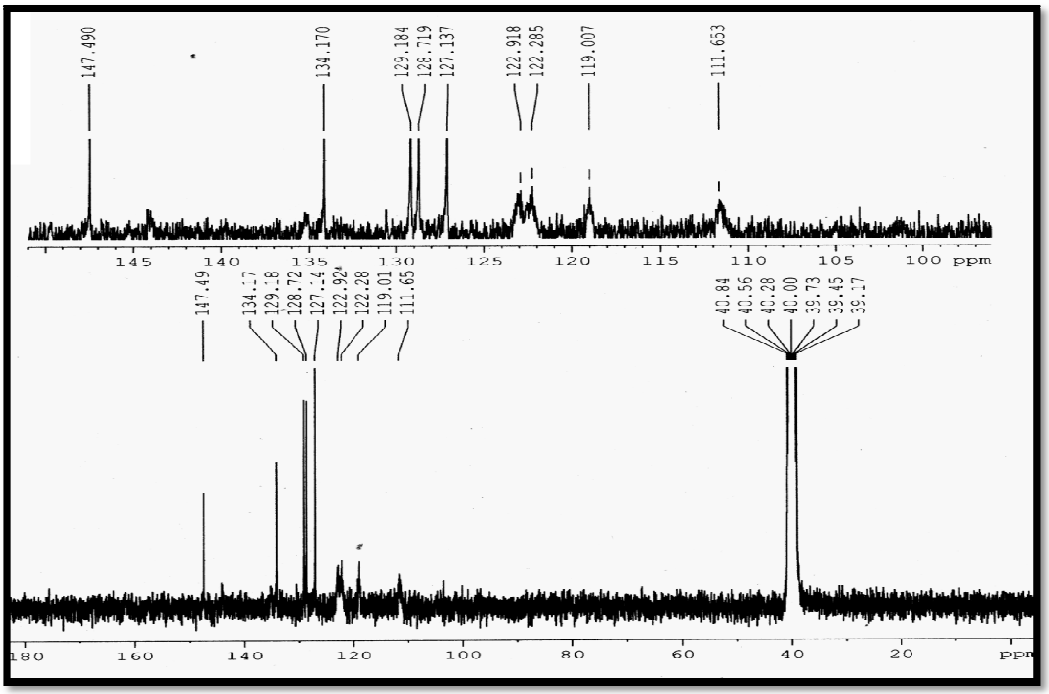


Fig.V.B.10.[13]C NMR spectrum of 2-(Thiophene-2yl)-1H-benzimidazole

V.B.7. References

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CHAPTER-VI

Synthesis of substituted imidazoles on titanium incorporated silica solid support

CHAPTER-VI

SECTION-A

VI.A. A brief review on imidazoles, synthesis and its applications

VI.A.1. Imidazole

Imidazole is an organic compound with the formula $(CH)_2N(NH)CH$. It is a colourless solid that dissolves in water to give mildly alkaline solution. In chemistry, it is an aromatic heterocycle, classified as a diazole and belongs to alkaloid family. The imidazoles substructure contributes important roles in biological system such as this ring system is present in important biological building-blocks, such as histidine, and the related hormone histamine.

VI.A.2. Structure

Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because the proton can be located on either of the two nitrogen atoms. Imidazole is a highly polar compound, as evidenced by a calculated dipole of 3.61D. It is highly soluble in water. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. The resonance structures of imidazole (**1**) are shown below:

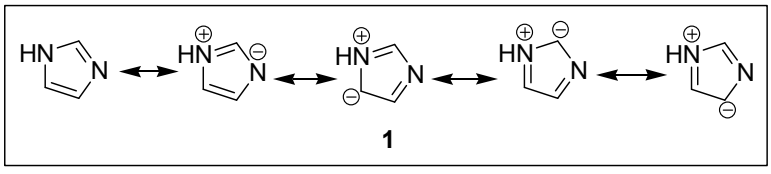


Fig.VI.A.1. Imidazole

VI.A.3. Biological importance of imidazole derivatives

Imidazole is strongly associated many important biologically active molecules. The most important is the amino acid histidine (**fig.VI.A.2**) which has an imidazole side chain. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of haemoglobin. Histidine can be decarboxylated to histamine, which is also a common biological compound. It is a component of the toxin

that causes urticaria, which is another name for allergic hives. Imidazole has become an important part of many pharmaceuticals. Synthetic imidazoles are present in many fungicides and antifungal, antiprotozoal, and antihypertensive medications. It is present in the anticancer medication mercaptopurine, which combats leukemia by interfering with DNA activities.

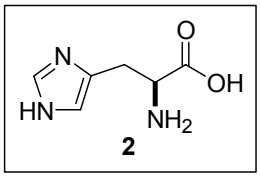


Fig.VI.A.2. Amino acid histidine

The suitably substituted imidazole derivatives are valuable in treatment of many systemic fungal infections. Imidazoles belong to the class of azole antifungals, which includes eprosartan (**1**), econazole (**2**), trifenagrel (**3**), isoconazole (**4**), omoconazole (**5**), tioconazole (**6**) etc (**fig.VI.A.3.**).

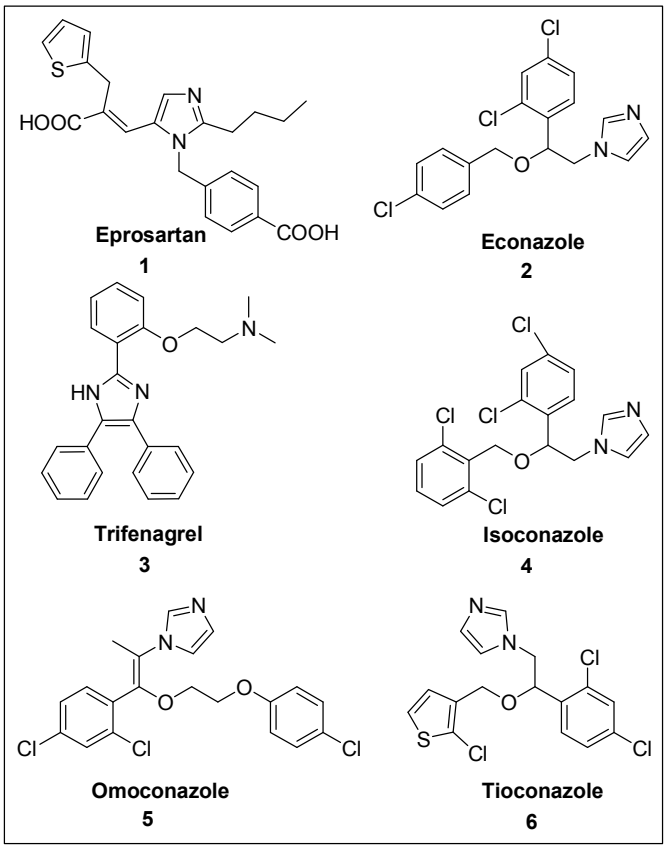


Fig.VI.A.3. Example of imidazole drugs

VI.A.4. Industrial applications

Imidazole has been used extensively as a corrosion inhibitor on certain transition metals, such as copper. Preventing copper corrosion is important, especially in aqueous systems, where the conductivity of the copper decreases due to corrosion. Many compounds of industrial and technological importance contain imidazole derivatives. The thermostable polybenzimidazole PBI contains imidazole fused to a benzene ring and linked to benzene, and acts as a fire retardant. Imidazole can also be found in various compounds that are used for photography and electronics.

VI.A.5. Application of imidazoles in organic synthesis

As imidazole moiety is associated with many bioactive useful organic compounds, it plays a useful starting material for the synthesis of wide range of nitrogen containing physiologically active natural and synthetic compounds (**fig.VI.A.4.**).[1] Due to the presence of two nitrogen atom, the suitable derivatives of the imidazole act as important ligand to many transition metals which are useful for the numerous organic transformations and sometimes used for the metal sensing fluorescence. It is a useful organic counterpart for the preparation of ionic liquids. Now days, imidazoles is also used as organo-catalyst for considerable organic transformation.

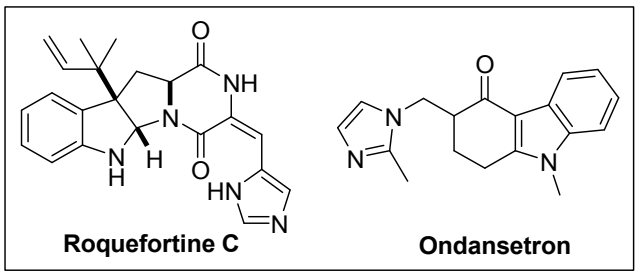
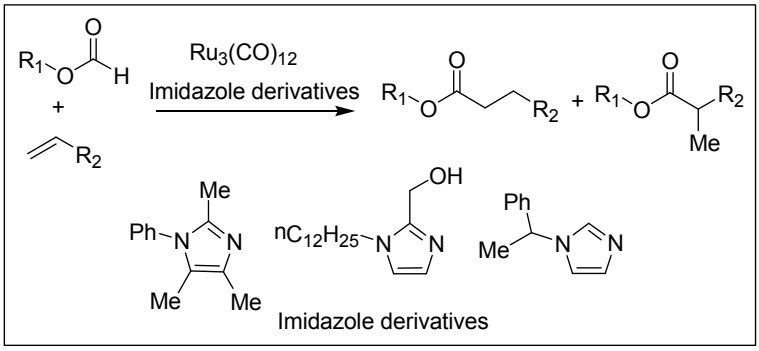


Fig.VI.A.4. Imidazole ring containing physiologically active compounds

VI.A.6. Roles of imidazoles as ligands

Various derivatives of imidazole are used as a useful ligand form considerable number of transition metals. Kei Manabe et al.[2] reported the Ru-catalyzed hydroesterification of alkenes using formates, affording one-carbon elongated esters in high yields using imidazole derivatives as a effective ligand (**scheme.VI.A.1.**). Aaron Aponick et al.[3] reported the design, preparation and implementation of an imidazole-based chiral biaryl

P, N-ligand for asymmetric catalysis where the ligand found to perform exceptionally well in the enantioselective coupling. Roman Sívek, Filip Bureš et al.[4] reported the synthesis and application in asymmetric synthesis of imidazole based potential bi-and tridentates ligand.



Scheme.VI.A.1. Ru-catalyzed hydroesterification of alkenes

VI.A.7. Use of imidazole for the preparation of ionic liquids

Ionic liquids are defined as molecules containing a permanent charge and a melting point below 10 ^{o}C. Recently, ionic liquids have proved quite versatile for enabling a range of exciting applications. In general, the more common ionic liquids possess an organic cation and an inorganic anion, although this is not a requirement. Ionic liquids have also been quite popular recently due to their potential application as green chemical reaction solvents. The imidazole ring is a very versatile scaffold for ionic liquids. The ring is easily ionized upon quaternization of the tertiary nitrogen atom, resulting in a permanent positive charge.

Imidazole-based ionic liquids have found uses in several applications including potential water treatment agents due to their ability to coordinate with metal atoms, and they are also recognized for their potential as green organic solvents due to their lack of volatility.[5] Furthermore, a unique combination of various alkyl substituents and counteranions enables tuning of the properties of the liquid to meet the demands of the application. The first imidazole based ionic liquid was 1-ethyl-3-methylimidazolium chloride. Later on anion exchange with more hydrolytically stable anions such as BF_4^-, PF_6^-, NO_3^-,SO_4^-, or acetate that the resulting ionic liquids were quite stable.[6] This development led to the birth of the imidazole-based modern day ionic liquid.

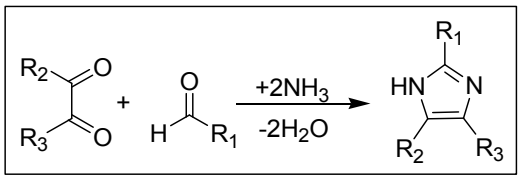
VI.A.8. Role of imidazoles in catalysis

Imidazole and imidazole tuned with transition metal shows highly effective catalytic properties for numerious organic transformations. Yasuhiro Uozumi et al.[7] reported self-assembled poly(imidazole-palladium) as highly active reusable catalyst for the allylic arylation/alkenylation of allylic acetates and carbonates with tetraarylborates, arylboronic acid, and alkenyl boron reagents in alcohol and/or water. Later on, the same group again reported the self-assembled copper sulfate and a poly-(imidazole−acrylamide) amphiphile as highly efficient solid phase catalyst for the Huisgen 1, 3-dipolar cycloaddition of a variety of alkynes and organic azides, including the threecomponent cyclization of a variety of alkynes, organic halides, and sodium azide.[8] M. P. Kaushik et al.[9] reported an simple imidazole catalyzed selective monoacylation of symmetrical aliphatic primary and secondary diamine.

Marc L. Snapper et al.[10] reported use of an amino acid based imidazole catalyst for the enantioselective catalytic silylation of racemic diols which offers access to enantiomerically enriched monosilylated regioisomers.

VI.A.9. Classical methods for the preparation of imidazoles

Imidazole was first synthesized by Heinrich Debus in 1858 by the reaction of glyoxal and formaldehyde in ammonia to form imidazole but various imidazole derivatives had been discovered as early as the 1840s (**scheme.VI.A.2**).[11]



Scheme.VI.A.2. Classical method for the synthesis of imidazoles

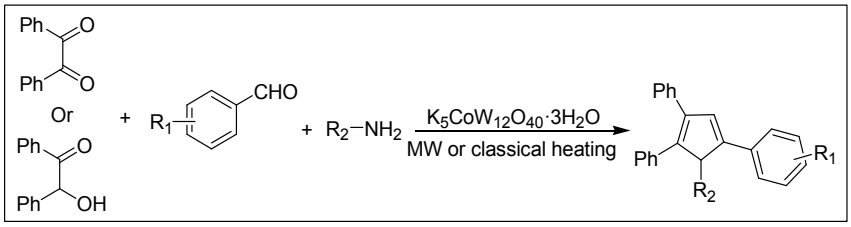
VI.A.10. Modern method for the synthesis of imidazoles

Because of diverse biological, pharmacological and material properties associated with imidazole moiety, the researcher devoted to develop more convenient synthetic protocol for the present day demand. In the last decades, the numerous protocols have been developed for the synthesis of multisubstituted imidazoles by using diverse catalytic system. The modern methods consist of multicomponent reaction between 1, 2-

diketone/ α-hydroxy ketone, aldehyde, and ammonium atetate under different catalytic conditions. The recent literature reveals that, the precursor other than 1, 2 diketone, α-hydroxy ketone or aldehydes have been also used for the direct synthesis of substituted imidazole under different catalytic system.

VI.A.10.1. Synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles

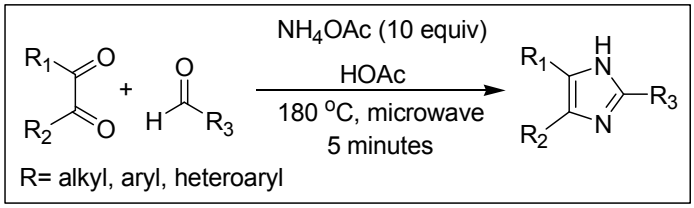
Literature review revealed that researcher have developed considerable synthetic protocols for the synthesis of tetrasubstituted imidazoles by four component condensation of benzil/ α-hydroxy ketone, aromatic aldehydes, primary amines in the presence of ammonium acetate such as synthesis of tetrasubstituted imidazoles catalyzed by zeolite HY and silica gel without any solvent under microwave irradiation,[12] potassium dodecatugstocobaltate trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$) catalyzed one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles under conventional heating and microwave irradiation (**scheme.VI.A.3**),[13] Keggin-type heteropolyacids catalyzed four-component one-pot synthesis of tetrasubstituted imidazoles,[14] silica-supported boron trifluoride ($BF_3.SiO_2$) catalyzed one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles,[15] silica-bonded propylpiperazine-N-sulfamic acid catalyzed an efficient procedure for the preparation in chloroform,[16] 3-Methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulphate [$(CH_2)_4SO_3HMIM$] [HSO_4], a Brønsted acidic ionic liquid catalyzed synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using benzil, an aromatic aldehyde, and a primary amine in the presence of ammonium acetate under solvent-free condition,[17] trifluoroacetic acid (TFA) catalyzed synthesis of various tetrasubstituted imidazoles under microwave-irradiation and solvent-free conditions,[18] $HClO_4$–SiO_2 catalyzed one-pot, solvent-free synthesis of tetrasubstituted imidazoles.[19]



Scheme.VI.A.3. Potassium dodecatugstocobaltate trihydrate catalyzed one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles

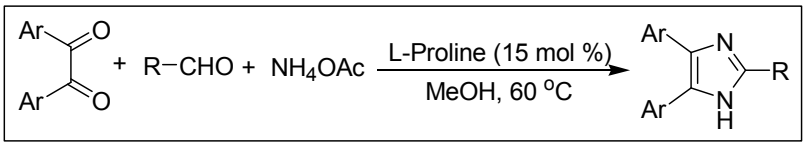
VI.A.10.2. Synthesis of 2, 4, 5-trisubstituted imidazoles

The development of simple, efficient and environmentally benign chemical process or methodologies for widely used pharmacophores from readily available reagents and catalysts are the major challenges for the chemist world over. Literature review revealed that numerous protocols have been developed for the synthesis of 2, 4, 5-trisubstituted imidazoles. Scott E. Wolkenberg et al.[20] have reported the synthesis of alkyl-, aryl-, and heteroaryl-substituted imidazoles from 1, 2-diketones and aldehydes in the presence of NH_4OAc under microwave irradiation (**scheme.VI.A.4.**).



Scheme.VI.A.4. Synthesis of imidazole derivatives under microwave irradiation

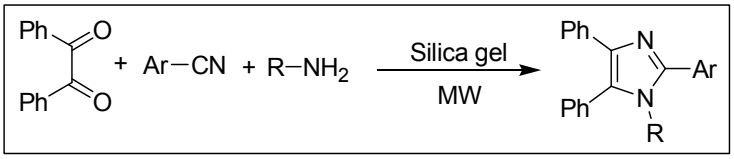
The reported synthetic routes to 2, 4, 5-trisubstituted imidazoles are multicomponent reaction between benzil or benzoin with aldehydes and ammonium acetate under diverse catalytic or reaction contions such as Cu(II) nitrate impregnated zeolite,[21] MoO_3/SiO_2 a recyclable solid acid,[22] silica-supported titanium tetrachloride under solvent-free conditions using conventional heating or microwave irradiation,[23] silica-sulfuric acid catalyzed synthesis in water,[24] L-proline (**scheme.VI.A.5.**),[25] $InCl_3.3H_2O$,[26] $ZrCl_4$,[27] $NiCl_2.6H_2O$ supported onto acidic alumina,[28] ceric (IV) ammonium nitrate in aqueous media under ultrasound at room temperature,[29] DABCO,[30] Fe_3O_4 nanoparticles,[31] bioglycerol-based recyclable carbon catalyst,[32] sulfated tin oxide.[33]



Scheme.VI.A.5. L-Proline catalyzed synthesis of substituted imidazoles

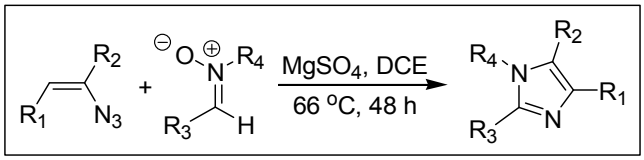
VI.A.10.3 Miscellaneous approach for the synthesis of substituted imidazoles

The literature survey reveals that the substituted derivatives of imidazole can also be prepared from the combination of 1, 2-diketo and non-carbonyl functions or carbonyl groups and other than 1, 2-diketo compounds. Saeed Balalaie et al.[34] have reported one-pot condensation of benzil, benzonitrile derivatives and primary amines on the surface of silica gel under solvent-free conditions and microwave irradiation[34] (**scheme.VI.A.6.**).



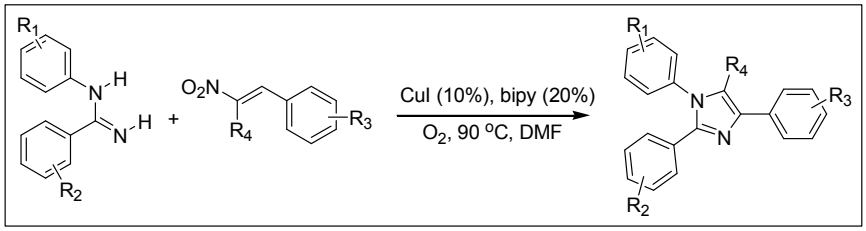
Scheme.VI.A.6. Synthesis of tetrasubstituted imidazoles under solvent-free conditions and microwave irradiation

Andrew P. Combs et al.[35] reported microwave-assisted synthesis of 2, 4, 5-triaryl-imidazole directly from the keto-oxime. Bao Hu et al.[36] have reported catalyst free a convenient method for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles from readily accessible 2-azido acrylates and nitrones (**scheme.VI.A.7.**).



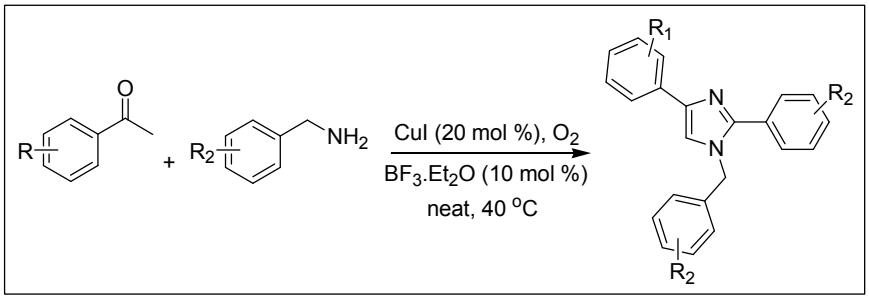
Scheme.VI.A.7. Synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles from readily accessible 2-azido acrylates and nitrones

Transition metal catalyzed cycloaddition of suitable functional groups is also an alternative way for the construction of these derivatives. Yoshinori Yamamoto et al. [37] have reported the synthesis of imidazoles through the copper-catalyzed cross-cycloaddition between two different isocyanides. Bao-Hua Chen et al.[38] have reported copper catalyzed synthesis of substituted imidazoles via [3+2] cycloaddition (**scheme.VI.A.8.**).



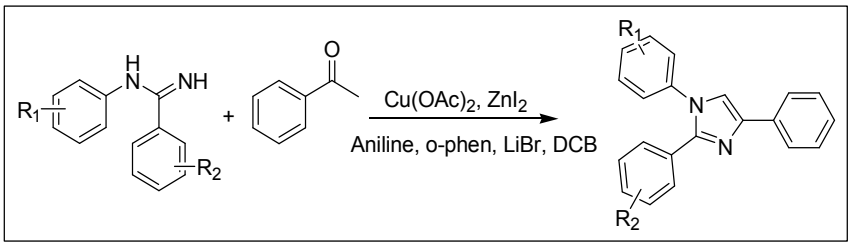
Scheme.VI.A.8. Copper catalyzed synthesis of substituted imidazoles

Shun-Jun Ji et al.[39] have reported CuI/$BF_3.Et_2O/O_2$-mediated synthesis of substituted imidazoles from ketone and benzyl amines via C(sp^3)-H bond functionalization (**scheme.VI.A.9.**).



Scheme.VI.A.9. CuI/$BF_3.Et_2O/O_2$-mediated synthesis of substituted imidazoles

Recently, Bao-Hua Chen et al.[40] have reported copper and zinc co-catalyzed efficient synthetic approach to imidazoles from amidines and arylketone via oxidative coupling of (sp^3)C-H bond and N-H bond (**Scheme.VI.A.10.)**.



Scheme.VI.A.10. Synthesis of imidazoles from amidines and arylketone via oxidative coupling of (sp^3)C-H bond and N-H bond

VI.A.11. Conclusion

The numerious methodologies have been developed for the synthesis of substituted imidazoles using diverse catalytic system. The starting materials other than 1, 2-diketo compounds are also well known in literature. But the loss of metal salts and solvents are the major draw-backs of most of the reported protocols. In view of wide applications of this moiety in the area of pharmaceuticals as well as in organic synthesis, author felt necessary to develop a mild, efficient and green protocol for their synthesis avoiding excess metal salt waste into the environment which reduces the chemical pollution.

VI.A.12. References

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CHAPTER-VI

SECTION-B

Synthesis of substituted imidazoles on titanium incorporated silica solid support

VI.B. Present Investigation

VI.B.1. Background of the present investigation

Imidazoles and their derivatives are regarded as important *N*-containing heteroaromatic compounds, were found in many bioactive compounds and natural products.[1] Suitable derivatives of imidazole act as important precursor for the natural product synthesis.[2] Among them, multi substituted imidazole provides significant core structure used in medicinal chemistry due to their wide spectrum of biological activities, such as glucagon receptor-antagonism,[3] anti-allergic,[4] anti-inflamatory,[5] analgesic,[6] cytotoxicity against several cancer cell lines.[7] Trifenagrel[8] is a potent 2, 4, 5-triaryl imidazole that reduces platelet aggregation in several animal species and humans. In recent years, substituted imidazoles are substantially used as ionic liquid[9] and ligand to transition metals[10]. Inspite of having numerous applications, more interestingly, imidazoles and self assembled polymeric imidazole complexes show the excellent catalytic activities for the various organic transformation.[11] The derivatives of this heterocycle has been in other area of research such as biological imaging,[12] fluorescence labelling agents[13] and chromophores for non-linear optics.[14]

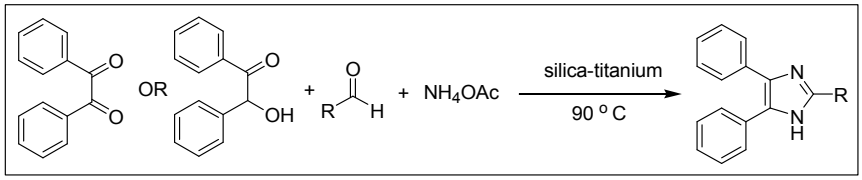
In view of the diverse biological, pharmacological and material properties associated with these derivatives, the development of more convenient synthetic protocol is highly encouraging for the present demand. In the last decades, the numbers of protocol have been developed for the synthesis of multisubstituted imidazoles by using diverse catalytic system, including silica gel or Zeolite HY,[15] $Cu(NO_3)_2$-zeolite,[16] $HClO_4$–SiO_2,[17] silica gel/$NaHSO_4$,[18] MoO_3-silica,[19] $TiCl_4$-silica,[20] silica-sulphuric acid,[21] L-proline,[22] $K_5CoW_{12}O_{40}.3H_2O$,[23] heteropolyacids,[24] molecular iodine,[25] BF_3-SiO_2,[26] $FeCl_3.6H_2O$,[27] $InCl_3.3H_2O$,[28] $ZrCl_4$,[29] ionic liquids,[30] $NiCl_2.6H_2O/Al_2O_3$,[31] CAN,[32] PEG,[33] DABCO,[34] Fe_3O_4 nanoparticles,[35] propylpiperazine N-sulfamic acid,[36] glycerol-based carbon catalyst,[37] sulphated tin oxide,[38] microwave irradiation,[39] and refluxing in acetic acid.[40] The recent literature reveals that, the precursor other than 1,2 diketone,

alpha hydroxy ketone or aldehydes have been also used for the direct synthesis of substituted imidazole under different catalytic system.[41]

However, the principal drawbacks of various reported protocols are non recyclable solid support or catalyst, use of expensive reagents, highly moisture sensitive metal salts, large amount of catalyst loading, tedious workup procedure, which in turn results in the generation of large amount of toxic metal salts and solvents into the environment.

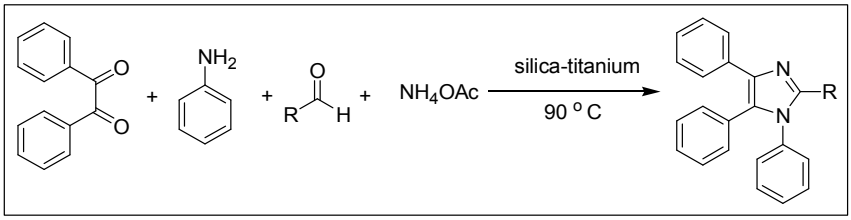
A present research area is lead by the development of environmental friendly protocol for the organic synthesis and transformations. In this context, researchers are devoting to developed protocol for solid phase – solvent free synthesis or the reaction in water. The major advantage of solid phase and aqueous media synthesis is no requirement of hazardous solvent which definitely reduce chemical pollution into the environment and in the same way, the cost of the work.

With this background, the development of new recyclable solid support to overcome these shortcomings and fulfil the criteria of mild, efficient and green protocol for the synthesis of these derivatives is an important task for the present demand of green and sustainable development. We report herein, one-pot synthesis of 2, 4, 5-trisubstituted imidazoles by multi-component reaction involving benzil/benzoin, aldehydes and NH_4OAc using a new and recyclable silica-titanium solid support under solvent free condition (**scheme.VI.B.1**).



Scheme.VI.B.1. Synthesis of 2, 4, 5-trisubstituted imidazole under solvent free condition

The same solid support was found equally efficient for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazole (**scheme.VI.B.2**)



Scheme.VI.B.2. Synthesis of 1, 2, 4, 5-tetrasubstituted imidazole under solvent free condition

The demand of titanium based solid support or catalyst in the area of organic synthesis and transformation,[34] is continuously increasing. In order to find a possible applications and exploring the use of titanium based solid support into wide prospective, we report herein, one-pot synthesis of substituted imidazole on titanium incorporated silica solid support under solvent free condition.

VI.B.2. Results and discussion

In our initial studies towards the development of new solid support for the synthesis these derivatives, $TiCl_3$ (0.25 mmol) and silica gel (silica gel HF 254) (1g) were added successively in methanol (10 ml). The mixture was allowed to stir on magnetic stirrer at 70-80 ^oC for 5 h and then allowed to cool at room temperature, evaporated the solvent on rotary evaporator. The dried titanium based solid support was further activated by keeping in hot oven at 200 ^oC for 8 h and allowed to cool at room temperature and used for the desired transformation.

The model reaction comprising benzil (0.5 mmol), ortho hydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) on pure silica (1g) at room temperature gives no yield in 15 h, only starting material was recovered. Further gradual increase in reaction temperature up to 100 ^oC furnishes no significant yield (**table.VI.B.1.**).

Table.VI.B.1.

Model reaction on pure silica[a]

Entry	Temp (^{o}C)	Time (h)	Yield (%)[b]
1	r.t	15	NR[c]
2	40	15	NR
3	60	10	NR
4	80	10	trace
5	90	8	10-12
6	100	8	36

[a]Reaction of benzil (0.5 mmol), ortho hydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) in pure activated silica (1gm). [b]Isolated yield. [c]No reaction.

Only trace amount of the desired product was formed when the same reaction was carried out on titanium incorporated silica at room temperature (**table.VI.B.2.**). The gradual increase in temperature up to 90 ^{o}C found that the titanium-silica is catalyzing the reaction efficiently. The transformation is excellent at 90 ^{o}C (**table.VI.B.2.**). It is clear from the (**table.VI.B.1.**) and (**table.VI.B.2**) that the catalytic activity of the solid support is due to titanium incorporation. We attempted reusing the solid support to check its efficiency for the second reaction run and found no significant loss of its activity. For the reusability of solid support, the product was extract from reaction mixture in ethyl acetate, washed the solid support by methanol (10x2 ml), several times by water and reactivated under vacuum at 200 ^{o}C for 8 h. The the catalytic activity of used solid support were checked for five consecutive run and found almost equally active for all consecutive runs (**table.VI.B.3**). The invariable catalytic activity after recycling indicates that no significant loss of titanium from solid support.

Table.VI.B.2

Optimization of temperature[a]

Entry	Temp (^{o}C)	Time (h)	Yield (%)[b]
1	r.t	4	trace
2	40	4	18
3	60	4	38
4	70	4	57
5	80	4	76
6	90	4	92

[a]Reaction of benzil (0.5 mmol), orthohydroxy benzaldehyde (0.5mmol) and ammonium acetate (2 mmol) on titanium-silica solid support under solvent free condition. [b]Isolated yield.

Table.VI.B.3

Screening of catalyst recycling[a]

Entry	Time (h)	No. of runs	Yield (%)[b]
1	4	1	92
2	4	2	92
3	4	3	90
4	4	4	88
5	4	5	87

[a]Reaction of benzil (0.5 mmol), orthohydroxy benzaldehyde (0.5mmol) and ammonium acetate (2 mmol) on titanium-silica solid support at 90 ^{o}C under solvent free condition. [b]Isolated yield.

It is very clear from the SEM images, that the pure silica is converted into titanium-silica. The SEM images of pure silica (**fig.VI.B.1**), freshly prepared titanium-silica (**fig.VI.B.2**) and reused titanium-silica (**fig.VI.B.3., VI.B.4., VI.B.5.**) were compared for the conformation. The dissimilarities in surface morphology of pure silica and titanium-silica clearly indicate the incorporation of titanium in silica. The similar surface morphology of titanium-silica on recycling up to five consecutive runs also signify no loss of titanium from titanium-silica solid support.

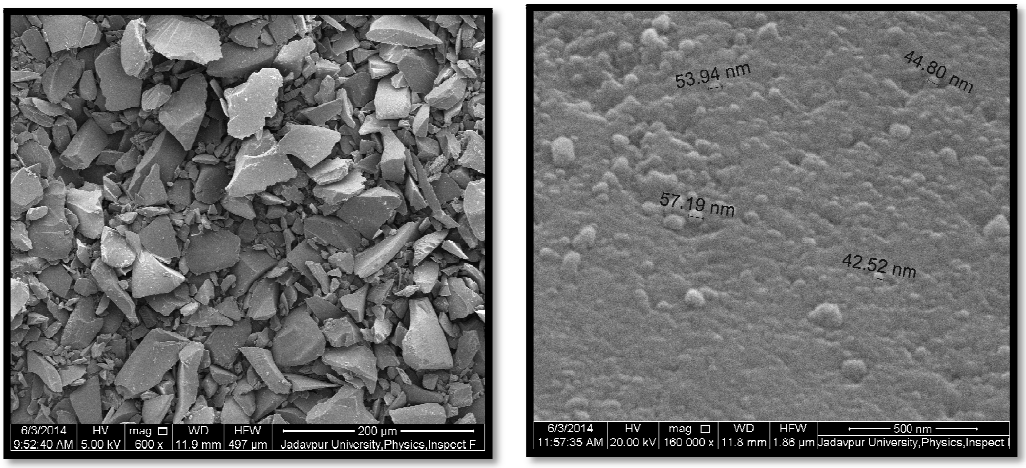


Fig.VI.B.1. SEM images of pure silica

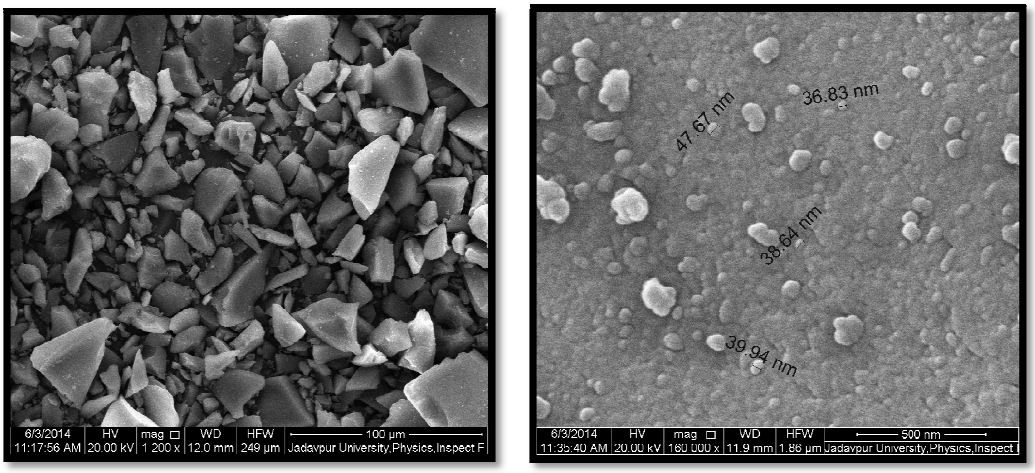


Fig.VI.B.2. SEM images of freshly prepared titanium-silica solid support

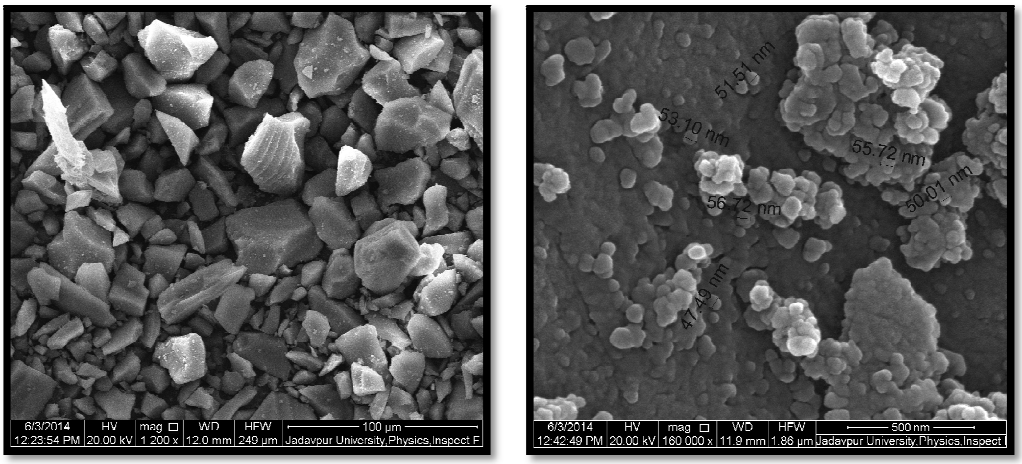


Fig.VI.B.3. SEM images of titanium-silica after first reaction run

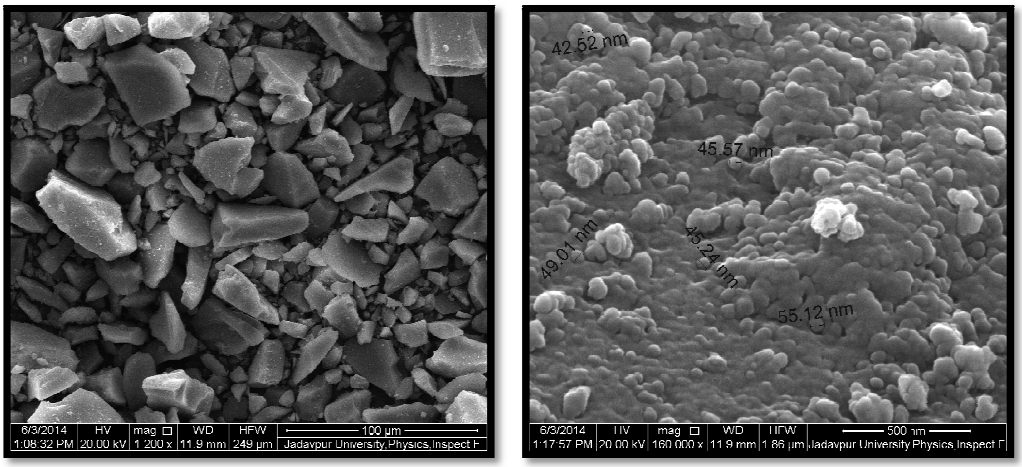


Fig.VI.B.4. SEM images of titanium-silica, after second reaction run

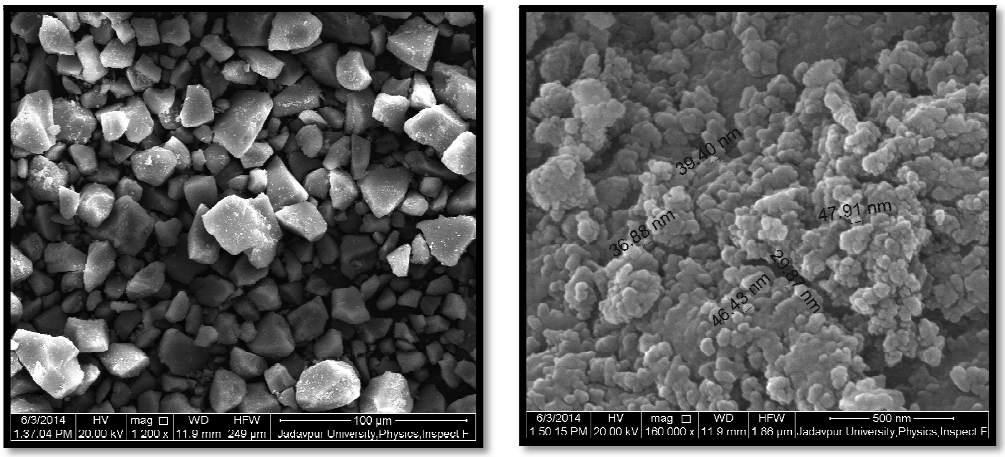


Fig.VI.B.5. SEM images of titanium-silica after fifth reaction run

The further characterization by EDX (**fig.VI.B.6-VI.B.10.**) and elements mapping clearly confirm that incorporation of titanium into silica. The comparative EDX studies also shows small leaching of titanium during recycling (**table.VI.B.4**). The EDX elemental mapping and EDX comparative data of the pure silica (a) freshly prepared titanium-silica (b) and recycled titanium-silica provides an excellent evidence for the presence of titanium after recycled (**fig.VI.B.11-VI.B.15.**). The small loss of titanium during recycle indicates the existence of strong interaction between titanium and silica.

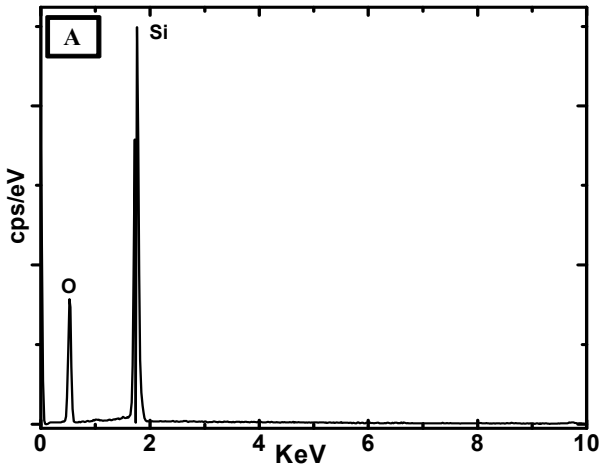


Fig.VI.B.6. Atom composition according to EDX measurements of pure silica

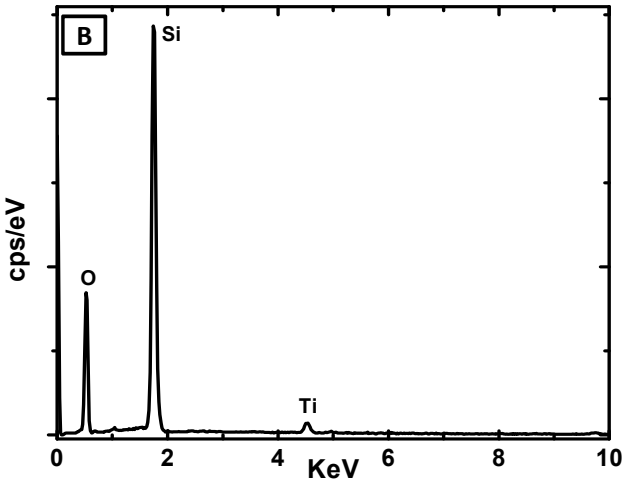


Fig.VI.B.7. Atom composition according to EDX measurements of freshly prepared titanium-silica

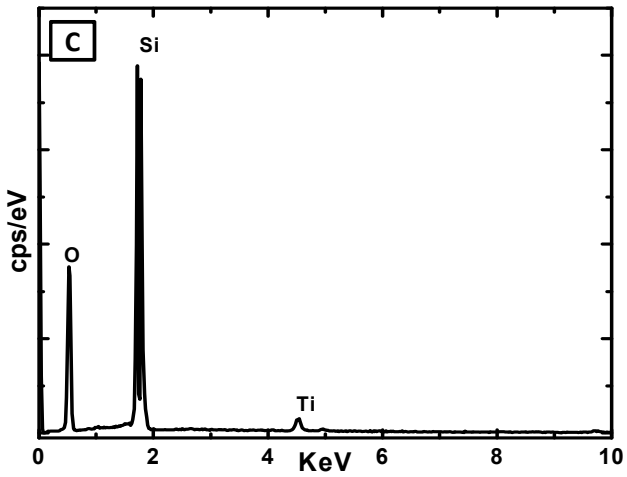


Fig.VI.B.8. Atom composition according to EDX measurements of titanium-silica after first reaction runs

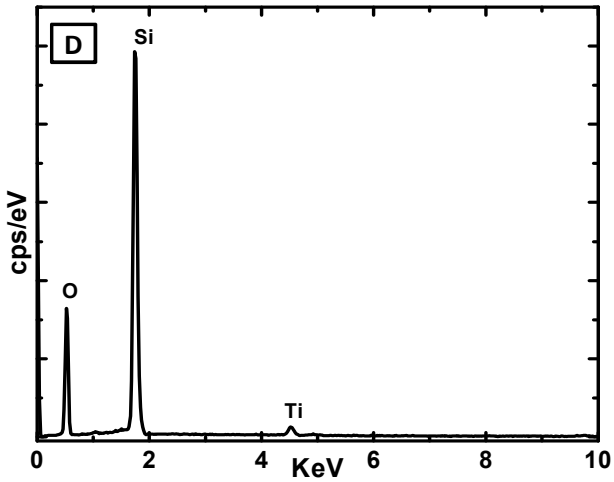


Fig.VI.B.9. Atom composition according to EDX measurements of titanium-silica after second reaction runs.

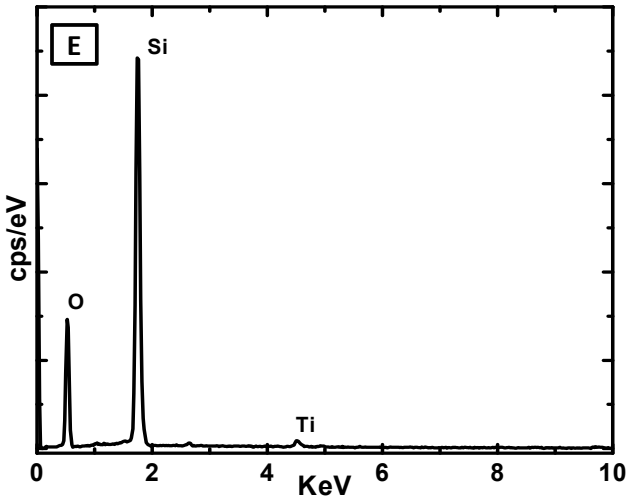


Fig.VI.B.10. Atom composition according to EDX measurements of titanium-silica after fifth reaction runs

Table.VI.B.4.

Comparative profile of the atom compositions according to EDX measurements

Support	Elements	Weight (%)	Atomic (%)	Total
Silica	O	53.26	66.67	100.00
	Si	46.74	33.33	
Fresh Si-Ti support	O	52.37	66.67	100.00
	Si	43.61	31.62	
	Ti	4.02	1.71	
Recycled Si-Ti support (second run)	O	52.43	66.67	100.00
	Si	43.81	31.73	
	Ti	3.77	1.60	
Recycled Si-Ti support (After fifth run)	O	52.70	66.67	100.00
	Si	44.78	32.27	
	Ti	2.52	1.06	

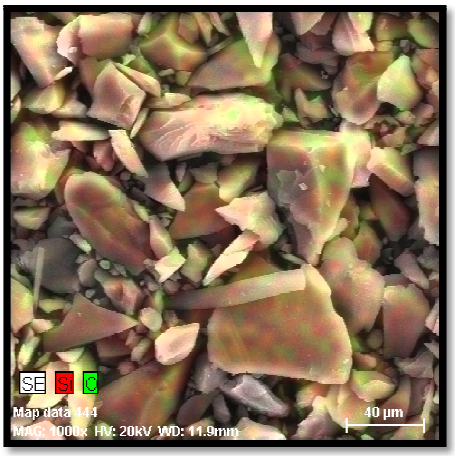


Fig.VI.B.11.

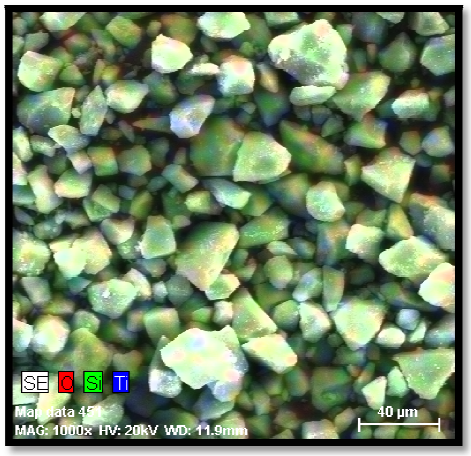


Fig.VI.B.12.

Fig.VI.B.11.= Elements mapping of pure silica

Fig.VI.B.12.= Elemental mapping of freshly prepared titanium-silica solid support

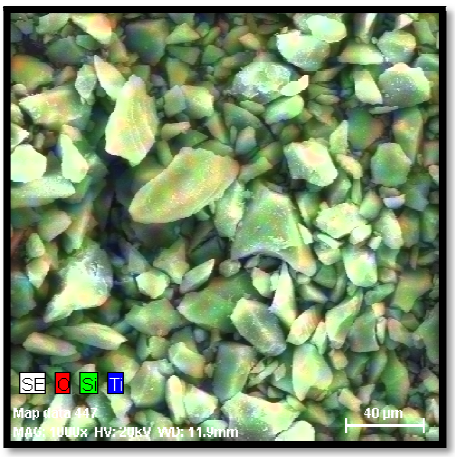


Fig.VI.B.13.

Fig.VI.B.14.

Fig.VI.B.13.= Elemental mapping of titanium-silica after first reaction run

Fig.VI.B.14.= Elemental mapping of titanium-silica after second reaction run

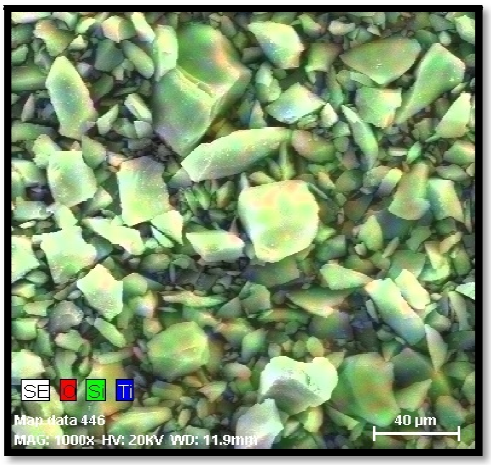
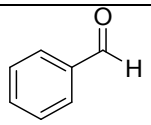
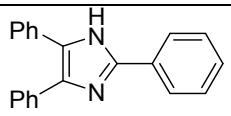
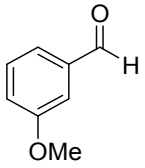
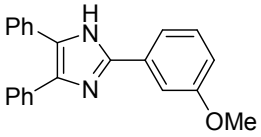
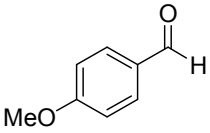
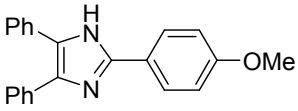
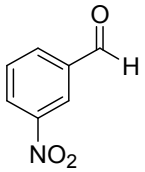
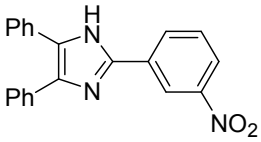
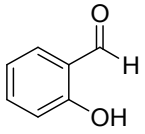
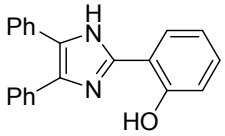
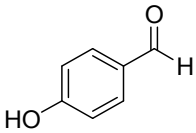
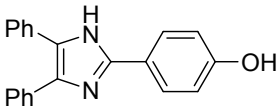
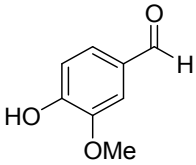
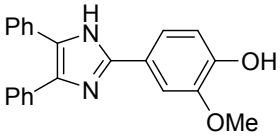
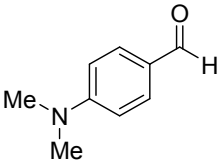
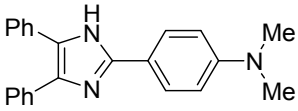
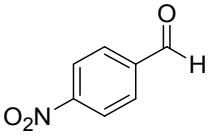
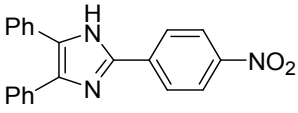


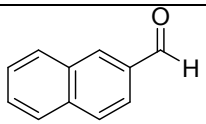
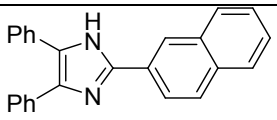
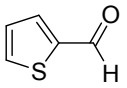
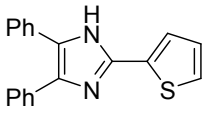
Fig.VI.B.15. Elemental mapping of titanium-silica after fifth reaction run

The general applicability of the solid support was examined by the synthesis of wide varieties of imidazole derivatives. The synthesis were carried out by taking benzil/benzoin (0.5 mmol), aldehyde (0.5 mmol) and NH_4OAc (2 mmol) on freshly prepared titanium-silica (1g) at 90 ^oC under solvent free condition. The results are summarized in (**table.VI.B.5**).

Table.VI.B.5

Synthesis of 2, 4, 5-trisubstituted immidazole

Entry	Aldehyde	Time (h)		Product	Yields (%)[b]	
		Benzil	Benzoin		Benzil	Bezoin
1		4	6		94	91
2		5	6		91	90
3		5	6		90	88
4		4	5		93	91
5		4	5		92	88
6		5	6		87	86
7		6	8		84	82
8		6	8		89	86
9		4	5		90	88

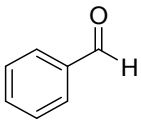
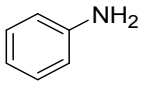
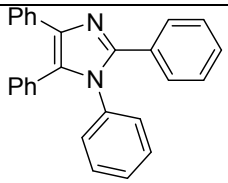
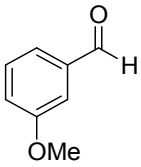
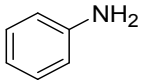
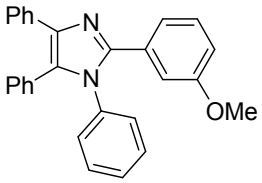
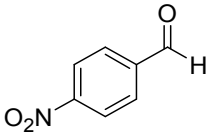
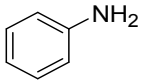
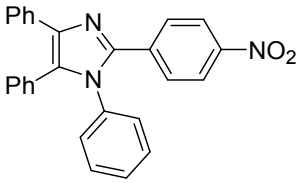
10		4	5		89	84
11		4	5		74	68

[b]Isolated yield

No loss of catalytic activity was found up to 30 days from the day of preparation of solid support. The solid support is also used to synthesized the 1, 2, 4, 5-tetrasubstituted imidazole (**scheme.VI.B.2**.) and found equally efficient for their synthesis (**table.VI.B.6.**).

Table.VI.B.6

Synthesis of 1, 2, 4, 5-tetrasubstituted imidazole

Entry	Aldehyde	Amine	Product	Yield (%)[b]
1				88
2				86
3				90

[b]Isolated yield

VI.B.3. Experimental

VI.B.3.1. Chemicals

All the chemicals which were used for the present investigation are listed in the **table.VI.B.7.** The details of the chemicals regarding their source and purity are summarised in **table.VI.B.7.**

Table.VI.B.7.

Chemicals used for the present investigation

Entry	Chemical	Source	Purity (%)
1	Benzaldehyde	Sigma-Aldrich	98
2	3-Methoxybenzaldehyde	Chemical Book	97
3	4-Methoxybenzaldehyde	Sigma-Aldrich	98
4	3-Nitrobenzaldehyde	LOBA Chemie	98
5	2-Hydroxybenzaldehyde	S.D Fine	99
6	4-Hydroxybenzaldehyde	S.D Fine	98
7	3-Methoxy-4-hydroxybenzaldehyde	S.D Fine	99
8	N,N-dimethyl-4-aminobenzaldehyde	Sigma-Aldrich	99
9	4-Nitrobenzaldehyde	LOBA Chemie	99
10	2-Napthaldehyde	Sigma-Aldrich	98
11	Pyridine-2-carboxaldehyde	Sigma-Aldrich	99
12	2-Thiophene-carboxaldehyde	Sigma-Aldrich	98
13	Benzil	SRL	98
14	Benzoin	SRL	98
15	Aniline	SRL	99.5
16	Ammonium acetate	LOBA Chemie	98
17	Titanium trichloride	LOBA Chemie	15 % solution
18	Sodium sulphate anhydrous	SRL	99.5
19	Petroleum ether	Thomas Baker	98
20	Ethyl acetate	Thomas Baker	99
21	Methanol	SRL	99.8
18	Silica gel 254 HF	SRL	-
19	Silica gel 60-120 mesh for column	SRL	-

20	Silica gel for TLC	SRL	-
24	Potassium bromide for IR	Merck	99
25	$CDCl_3$ for NMR	ACROS	99.8
26	DMSO-d_6 for NMR	SRL	99.8

VI.B.3.2. Reaction procedure and purification

VI.B.3.2.1. Synthesis of 2, 4, 5- trisutituted imidazole

Benzil/benzoin (0.5 mmol), aldehyde (0.5 mmol) and ammonium acetate (2 mmol) were mixed intimately with titanium-silica (1.0 g). The mixture mixed intimately in motor and pestle. The resulting mixture was poured in round bottom flask (50 ml) and allowed to stir on magnetic stirrer at 90 ^oC for appropriate time (table 5). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3x15 ml) washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate as eluent to afford pure compound.

VI.B.3.2.2. Synthesis of 1, 2, 4, 5-tetrasubstituted imidazole

Benzil (0.5 mmol), aldehyde (0.5 mmol), amine (0.5 mmol) and ammonium acetate (1 mmol) were mixed intimately with titanium-silica (1.0 g). The mixture was mixed intimately in motor and pestle. The resulting mixture was poured in round bottom flask (50 ml) and allowed to stir on magnetic stirrer at 90 ^oC for appropriate time (table 6). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3x15 ml) washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate as eluent to afford pure compound.

VI.B.3.3. Preparation of titanium-slica solid support

To a solution of $TiCl_3$ (0.25 mmol) in methanol (10 ml) at 70-80 ^oC, silica gel (1 g, 254 HF) was added. The mixture was allowed to stirrer at 70-80 ^oC for 5 h. The solvent was evaporated rotary evaporator and solid mass was kept in hot oven at 200 ^oC for 8 h and allowed to cool at room temperature and used for the desired transformation.

VI.B.3.4. Catalyst recycling

After the completion of the reaction, the catalyst was washed with methanol (2x25 ml) followed by washing with water (2x25 ml) and the solid mass was kept in hot oven at 200 ^{o}C for 8 h. The resulting recycled solid support was used for the reactions.

VI.B.3.5. Spectroscopic measurements

IR spectra were recorded on KBr disc in the range 4000-400 on Shimadzu FT-IR 8300 Spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal standard. SEM images were taken in inspect F50 SEM, SE detector R580, emission current during analysis was 163.2 micro ampere. EDX were recorded in nano bruker, Xflash detector 410-M, bruker. Mass spectra were recorded on a JEOL-AccuTOF JMS-T100LC Mass Spectrometer.

VI.B.4. Conclusion

In summary, our investigation has established that efficient, solvent free, green synthesis of highly substituted imidazoles. The protocol has been found to be broadly applicable to wide varieties of aldehydes without significant variation in yield with aldehydes having different functional groups. The stability and recyclability of the solid support makes the present investigation greatly advantageous.

VI.B.5. Spectroscopic data

VI.B.5.1. 2, 4, 5-Triphenyl-1*H*-imidazole

Mp 272-274 ^{o}C; IR (cm^{-1}, KBr): 3043, 1489, 1461, 1128, 733, 689. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.71-7.96 (m, 13H) 8.52 (d, 2H, J=7.2Hz), ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 130.4, 132.4, 132.9, 133.4, 133.6, 133.8, 135.5, 150.7 ppm. m/z = 297 [M+1].

VI.B.5.2. 2-(3-Methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole

Mp 260-263 ^{o}C; IR (cm^{-1}, KBr): 3432, 1589, 1516. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 3.84 (s, 3H), 6.83-7.76 (m, 14H), 12.61 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 55.6, 110.4, 113.9, 117.8, 127.6, 128.8, 129.1, 130.1, 131.9, 135.3, 137.4, 145.6, 159.4 ppm.

VI.B.5.3. 2-(4-Methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole

Mp 227-229 ^{o}C; IR (cm^{-1}, KBr): 3051, 1656, 1541, 1251, 1174, 831, 763, 696. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 3.82 (s, 3H), 7.05 (d, 2H, J=8.1Hz), 7.31-7.53 (m, 10H), 8.02 (d, 2H, J=8.1Hz), 12.51 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 55.6, 114.5, 123.4, 127.1, 127.5, 128.1, 128.8, 146, 159.8 ppm.

VI.B.5.4. 2-(2-Hydroxyphenyl)-4, 5-diphenyl-1*H*-imidazole

Mp 208-210 ^{o}C; IR (cm^{-1}, nujol): 3186, 2923, 1261, 723. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 6.92-7 (m, 2H), 7.25-7.53 (m, 11H), 8.03-8.05 (d, 1H, J=7.5Hz), 12.96 (s, 1H),13.04 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 113.3, 117.3, 119.3, 125.4, 127.2, 127.5, 127.7, 128.8, 129, 129.2, 130.5, 130.7, 134, 134.5, 146.3, 157.1 ppm. m/z = 313 [M+1].

VI.B.5.5. 2-(4-Hydroxyphenyl)-4, 5-diphenyl-1*H*-imidazole

Mp 231-233 ^{o}C; IR (cm^{-1}, KBr): 3434, 3297, 1637, 1542. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 5.93 (d, 1H, J=8.7Hz), 6.31-6.42 (m, 6H), 6.52-6.59 (m, 5H), 6.97 (d, 2H, J=8.3Hz), 8.81 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 115.2, 120.9, 127.1, 127.7, 128.4, 145.8, 157.4 ppm.

VI.B.5.6. 2-(3-Nitrophenyl)-4, 5-diphenyl-1*H*-imidazole

Mp 302-304 ^{o}C; IR (cm^{-1}, KBr): 3452, 1646, 1588, 1519. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.65-7.29 (m, 12H), 7.94 (d, 1H, J=7.4Hz), 8.13 (d, 1H, J=7.5Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 126.7, 127.4, 127.9, 128.8, 129.9, 130.1 ppm.

VI.B.5.7. 2-(4-Nitrophenyl)-4, 5-diphenyl-1*H*-imidazole

Mp 195-197 ^{o}C; IR (cm^{-1}, KBr): 3451, 1643, 1583, 1522. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.25-8.43 (m, 14H), 12.59 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 123.2, 126.7, 126.9, 131.8, 147.3, 159.8 ppm.

VI.B.5.8. 2-(4-Dimethylaminophenyl)-4, 5-diphenyl-1*H*-imidazole

M.p.: 255-257 ^{o}C; IR (cm^{-1}, KBr): 3170, 2854, 1610, 1305, 723. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 2.96 (s, 6H), 6.794 (d, 2H, J=8.7Hz), 7.27-7.38 (m, 6H), 7.48-7.51 (m, 4H),7.91 (d, 2H, J=8.4Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 40.3, 112.3, 118.1, 126.8, 127.4, 128.1, 128.8, 133.4, 146.8, 150.8 ppm. m/z = 340 [M+1].

VI.B.5.9. 2-(3-Methoxy-4-hydroxyphenyl)-4, 5-diphenyl-1*H*-imidazole

^{1}H NMR (300 MHz, $CDCl_3$): δ, 3.88 (s, 3H), 6.83-6.85 (m, 2H), 7.25-7.33 (m, 8H), 7.52-7.55 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 56, 112, 112.8, 116, 118.8, 127.8, 128.6, 131.8, 145.4, 146.8, 148.6.

VI.B.5.10. 2-(2-Napthyl)-4, 5-diphenyl-1*H*-imidazole

Mp 269-272 ^{o}C; IR (cm^{-1}, KBr): 3047, 1500, 1450, 1411, 1110, 912, 813, 750, 696. ^{1}H NMR (300 MHz, DMSO-d_6) : δ, 7.24-7.59 (m, 13H), 7.93-8.02 (m, 3H), 8.26 (dd, 1H, J=1.5, 8.4Hz), 8.61 (s, 1H), 12.89 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 123.9, 124.1, 126.8, 127.1, 127.2, 127.6, 128.2, 128.3, 128.5, 128.7, 128.8, 129, 129.1, 131.4, 133.1, 133.4, 135.5, 137.8, 145.1.

VI.B.5.11. 2-(2-Thienyl)-4, 5-diphenyl-1*H*-imidazole

Mp 262-264 ^{o}C; IR (cm^{-1}, KBr): 3047, 1593, 1493, 765, 696. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.14-7.17 (m, 1H), 7.32-7.37 (m, 6H), 7.49-7.56 (m, 5H), 7.71 (d, 1H, J=3.6Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 124.8, 126.7, 128.2, 128.4, 128.9, 134.4, 142 ppm.

VI.B.5.13. 1, 2, 4, 5-Tetraphenyl-imidazole

^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.01-7.05 (m, 2H), 7.10-7.28 (m, 14H), 7.41-7.44 (m, 2H), 7.58-7.61 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 126.6, 127.4, 127.9, 128.12, 128.18, 128.2, 128.3, 128.4, 128.9, 129, 130.5, 130.6, 130.8, 131.1, 134.4, 137.1, 138.3, 146.9 ppm.

VI.B.5.14. 2-(3-Methoxy phenyl)-1, 4, 5-triphenyl imidazole

^{1}H NMR (300 MHz, $CDCl_3$): δ, 6.78-6.81 (m, 1H), 6.98-7.25 (m, 16H), 7.59-7.62 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ, 55, 113.5, 114.9, 121.4, 126.6, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 129.06, 129.09, 130.5, 130.9, 131, 131.6, 134.3, 137.1, 138.1, 146.7, 159.1 ppm.

VI.B.5.15. 2-(4-Nitrophenyl)-1, 4, 5-triphenyl imidazole

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (d, 2H, J=7.7 Hz), 7.19 (d, 2H, J = 8.2 Hz), 7.24-7.33 (m, 6H), 7.32-7.39 (m, 3H), 7.58-7.64 (m, 4H), 8.11 (d, 2H, *J* = 8.8 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.6, 127.4, 127.7, 128.6, 128.8, 128.8, 129.3, 129.4, 130, 131.3. ppm.

VI.B.6. Supporting spectra

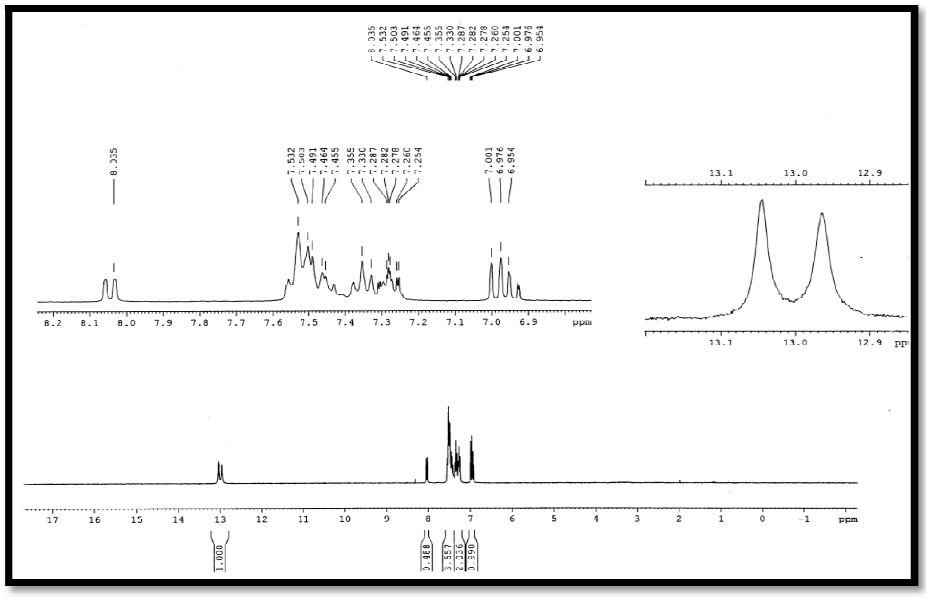


Fig.VI.B.16. ^{1}H NMR spectrum of 2-(2-Hydroxy-phenyl)-4,5-diphenyl-1*H*-imidazole

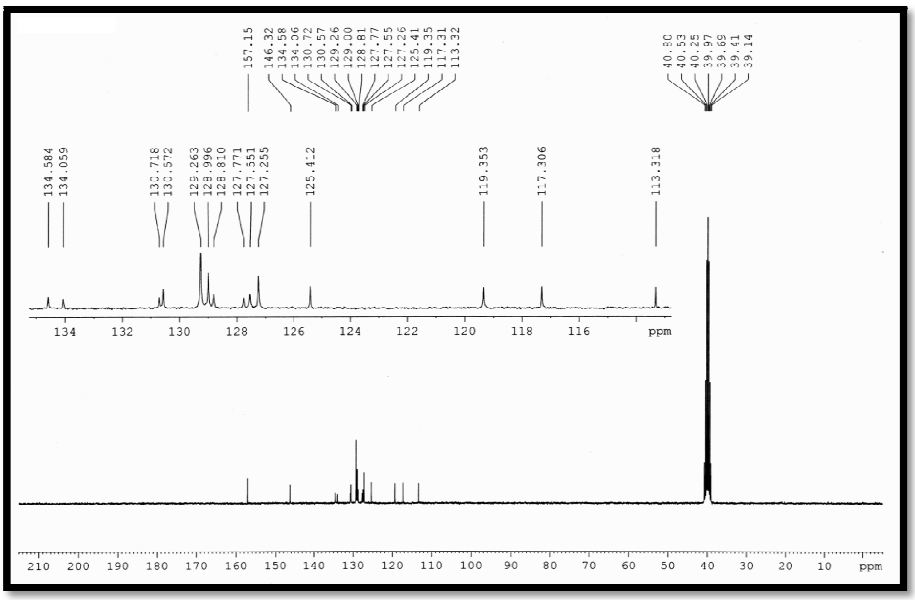


Fig.VI.B.17. ^{13}C NMR spectrum of 2-(2-Hydroxy-phenyl)-4,5-diphenyl-1*H*-imidazole

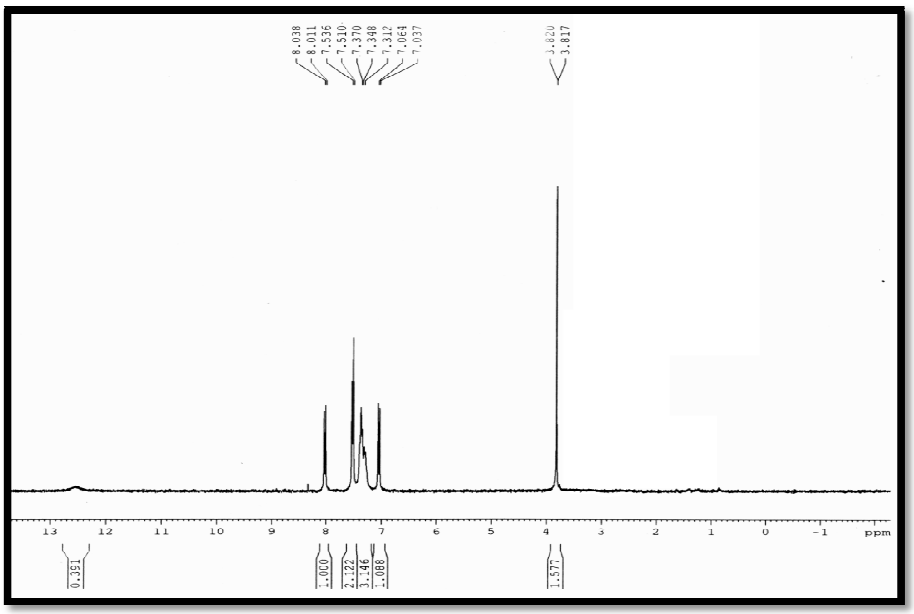


Fig.VI.B.18. [1]H NMR spectrum of 2-(4-Methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole

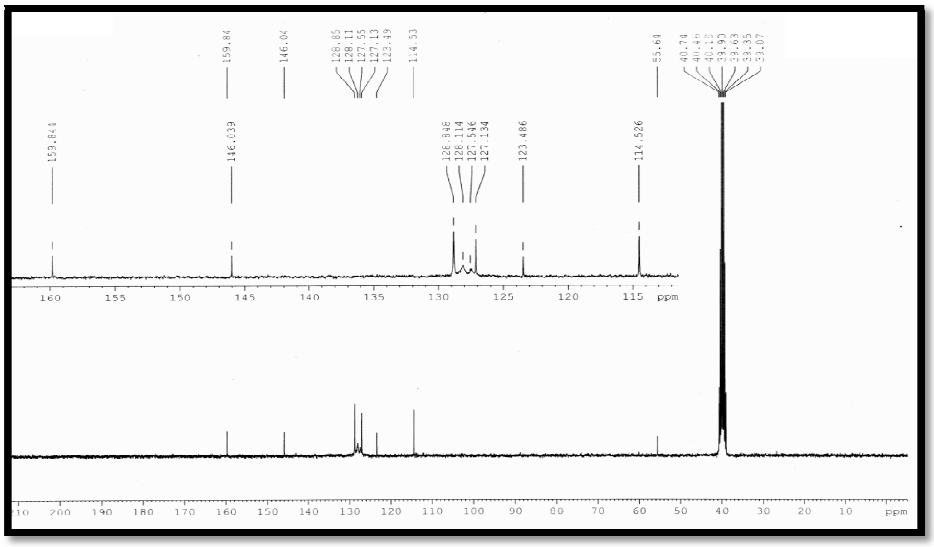


Fig.VI.B.19. [13]C NMR spectrum of 2-(4-Methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole

VI.B.7. References

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Chapter VI (Section-B)

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